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BLOOD TRANSFUSION REACTIONS: THEIR CAUSES AND PREVENTION

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THE LAST FEW YEARS have seen a tremendous increase in the use of blood transfusion, the fruition of three centuries of experiment and effort to treat disease by the administration of blood. The present-day, widespread use of this therapeutic measure coincides with the perfection of indirect methods of transfusion and the demonstration that these methods are eminently safe. Growing out from the indirect transfusion have come preserved blood transfusions and the transfusions of serum and plasma, all of which have greatly extended the scope and indications of blood transfusion. This vast increase in the numbers of transfusions given constitutes a challenge to reduce the incidence of untoward reactions to the lowest possible figures. Experience has shown that the causes of posttransfusion reaction are not inherent in the indirect methods, and that the control of such reactions demands centralized responsibility over all of the component steps of the transfusion operation, careful supervision of the numerous individual potential sources of error, and everlasting alertness to trace and eliminate breaks in technic. The purpose of this paper is to record the evolution of the present blood transfusion set-up at Michael Reese Hospital, tracing the gradual reduction of transfusion reactions, and to describe a modern blood transfusion department for a general hospital.

Organization of a Blood Transfusion Department.—The first requirement in establishing an adequate blood transfusion service is the creation of a definite department in which all of the phases of the operation are centralized, and under unified responsibility and control. If the typings and serologic examinations are done in one department, the cleansing and sterilization of

equipment in another, the drawing of blood in a third, to say nothing of the preparation of solutions, distillation of water, testing for the presence of pyrogenic substances, maintenance of donor lists, and keeping of records, it is obviously impossible to place responsibility for the occurrence of reactions, or to trace them to their source when they do appear.

The Blood Transfusion Department was established at Michael Reese Hospital in September, 1939. Separate quarters were allotted for this important work, and full-time personnel were assigned to carry out the various procedures incident to transfusions. The whole was placed under the direct and sole responsibility of the Director of the Serum and Transfusion Centers.

The Department continues to function as constituted with increasing satisfaction. All phases of the effort connected with the transfusion of blood, other than its actual injection, are performed in the Center. Here the blood groupings and compatibilities are determined, the Wassermann and Kahn tests made, and the other necessary laboratory examinations carried out. Professional donor lists are maintained and kept up to date; prospective donors are subjected to careful physical and hematologic examination; and family donors are selected and tested. All equipment for both the withdrawal and administration of blood is cleansed, assembled, wrapped, and sterilized in the Center. An adequate system of checks and cross-checks has been adopted to avoid infusing the blood into the wrong patient. If repeated reactions occur, an immediate reinvestigation of the entire procedure is made, with the aid of pyrogen tests, until the cause is found and eliminated.

Examination of Professional Donors.—Rigid requirements must be fulfilled before a person can be registered as a professional donor. Only healthy young males with good veins are selected. A careful history is taken of each candidate to rule out allergy, tuberculosis, malaria, and syphilis. A complete physical examination is then made. This includes a Wassermann and Kahn test, complete blood count, and differential blood smear examinations. Syphilis, secondary anemias, blood dyscrasias, and malaria are thus ruled out.

No professional donor is used more often than once in six weeks. The serologic tests are repeated every six weeks. In addition, the genitalia and the oral cavity are inspected immediately before blood is drawn for transfusion, in order to rule out recent syphilitic infections in which the serologic tests have not yet become positive.

Active donor lists comprising the various blood groups are maintained at all times. Prospective donors must remain on call, and within 20 minutes' reach of the hospital. Blood can thus be delivered to the patient within 30 minutes from the time the call is received in the Transfusion Center.

Examination of Family Donors.—Family donors who wish to provide blood are typed in the Transfusion Department and, if their blood group is found suitable, cross-compatibility tests are made. An immediate Kahn test is then done on the serum of the prospective donor. Family donors are obviously less amenable to the rigid control exerted over professional blood donors. It is not feasible to take a complete history, or to do a careful

physical and hematologic examination. Even the inspection of the genitalia and oral cavity is sometimes resented. These considerations, plus the time consumed in making the Kahn test, which takes about an hour, make family donors less desirable than professional ones aside, of course, from the economic factors.

Methods of Typing.—It goes without saying that careful blood group determinations are made upon all prospective patients and donors. Emphasis is placed upon the use of high-titer testing sera, to obviate the possibility of overlooking faint agglutinations, which may occur with low-titer sera. The International classification of the blood groups (Landsteiner) is used rather than that of Jansky or Moss, so that there will be no room for doubt or misunderstanding. The four groups, according to the International classification, are designated O, A, B, and AB, on the basis of the presence or absence of agglutinogens in the cells.

In addition to the blood typings, direct compatibility tests are made before each transfusion, matching and cross-matching the blood of the donor with that of the patient. These tests require very little additional time, and contribute materially to the safety of the transfusion. By rejecting all bloods that give the faintest question as to compatibility, the dangers of subgroup agglutination can be avoided.

Collection of Blood.—We are now using commercially prepared vacuum bottles exclusively for the collection of blood for transfusion. These bottles are hermetically sealed, and contain pyrogen-free 2.5 per cent sodium citrate in physiologic saline solution. A large-bore needle, equipped with a metal valve for regulating the rate of flow, is plunged through the stopper, into the bottle. Attached to the valve is a short length of rubber tubing which is armed with a No. 16-gauge blood-letting needle. With this apparatus, the procedure of drawing blood is exceedingly simple, and can be done by one person, unaided. The needle is introduced into the vein of the donor, the valve is opened slightly, and the blood is drawn by suction into the closed bottle. When the desired amount has been obtained, the needle is withdrawn from the arm, the valve-bearing needle is removed from the stopper, and a sealed, sterile flask of citrated blood is ready for administration or storage, as may be desired.

The administration of the blood is not a function of the Transfusion Center. The flask, properly prepared and labeled, is turned over to the clinical staff for injection. The technic thereof is equally simple. Another needle pierces the stopper, and is attached to an infusion set which is equipped with a fine-gauge metal filter and a drip-chamber. The bottle is inverted, the needle inserted into the vein of the patient, and the blood is given by the drip method in a manner similar to that of any intravenous infusion. The blood is, at all times during the procedure, kept in a closed system, and is not exposed to air or external sources of contamination, thereby minimizing greatly the potential causes of posttransfusion reaction.

Cleansing of Equipment—Pyrogen Tests.—It is now recognized that most

reactions are of the pyrogenic type, and that these are almost invariably due to the presence of contaminants in the apparatus or solutions. Proper cleansing of all parts of the equipment used is, therefore, of paramount importance in controlling transfusion reactions.[9] The glass and metal parts are cleansed relatively easily by washing in an acid solution, followed by distilled water. Care of rubber tubing is more difficult. In order to remove soluble pyrogens, it is necessary to boil the tubing first in a weak solution (0.1 or 0.2 per cent) of sodium hydroxide, and then in distilled water.

In order to be sure that no injurious foreign material remains in the tubing, a sample of the final washings in each batch is subjected to a *pyrogen test*. This consists of injecting an isotonic and sterile quantity of this material into the ear-vein of a rabbit. If pyrogenic substances are present, the animal will exhibit a typical pyrogenic reaction, with fever and, possibly, chills.

When the equipment has been proved to be satisfactorily clean, it is wrapped and autoclaved, and is then ready for use. Records are kept of all rubber tubing used, including the date of its preparation and the results of the pyrogen test. This facilitates checking back if reactions are reported.

Storage of Blood.—Most of the blood transfused at Michael Reese Hospital is administered immediately, or within a few hours after collection. While there are certain advantages in the use of stored blood, particularly in urgent cases, where the time factor is so important, there are also comparable objections due to the rapid disintegration of leukocytes, platelets and prothrombin, and to the shorter survival period of the stored red cells.[1, 7, 13] Other things being equal, we prefer the use of fresh blood, but a stock of refrigerated and citrated blood is kept on hand for emergency use.

It has been our policy to store blood for not longer than three days. If it is not used within that period, the plasma is drawn off under sterile conditions and pooled, to be used for plasma transfusions. When stored blood is used, no attempt is made to warm the refrigerated blood before injection because it has been shown that the administration of blood at low temperatures is not injurious, whereas the artificial heating of blood increases the risk of hemolysis.[2, 4]

Methods of Keeping Transfusion Records.—The importance of keeping detailed records of every transfusion cannot be too strongly emphasized. If the entire clinical situation surrounding the administration of blood is tabulated in a systematic manner, it becomes rather easy to trace the factors contributing to a posttransfusion reaction. The records are filed chronologically, with a cross-index arranged alphabetically (patients' names), as well as according to diagnosis or indication for transfusion. This information is acquired from several sources, including an abstract of the patient's chart, reports from interns and nurses, and by follow-up by the Transfusion Department. If a severe reaction is reported, a posttransfusion specimen of urine is examined for the presence of hemoglobin, and the clinical findings are correlated and compared with the pretransfusion course of the patient. The transfusion record chart used is herewith reproduced.

BLOOD TRANSFUSION REACTIONS

TRANSFUSION RECORD

#

Drawn _____ Given _____

Donor: Name _____ Address _____ Tel. _____
Age _____ Sex _____ Wgt. _____ Phys. Cond. _____ Rbc. _____ Hgb. _____
History _____

Recipient: Name _____ Address _____ Tel. _____
Age _____ Sex _____ Wgt. _____ Type _____ Allergy _____
Disease _____ Duration _____

Blood: Days Preserved _____ Type _____ Compatibility _____
Amount _____ Sterility _____
Kahn _____ Wassermann _____ Solutions added _____

Administration:
Duration: _____
Smoothness of flow _____
Amount actually given _____
Remarks: _____

EFFECTS (including preceding 48 hours)

Date	48–24 H before	24–0 H before	0–24 H after	24–48 H after	48–72 H after
R.B.C.					
H.G.B.					
T. (max.)					
T. (min.)					
P.					
R.					
B.P.					
Chills					
Cyanosis					
Gen. Cond.					
Urine					
Ashby Count					

Remarks: _____

BLOOD TRANSFUSION REACTIONS

Blood transfusion reactions may be classified simply as (1) pyrogenic or febrile; (2) allergic; and (3) hemolytic. Of these, the most frequent by far are the pyrogenic reactions. These consist essentially of a chill coming on during or shortly after the transfusion, followed by a sharp rise in temperature, which returns to normal within 24 or 48 hours. We consider a major pyrogenic reaction one in which there is a rise in temperature of at least two degrees above the pretransfusion level. If the temperature elevation is less than two degrees, it is considered a minor reaction. Pyrogenic reactions are not followed by jaundice, urinary retention, or hemoglobinuria. These phenomena indicate an incompatibility or hemolytic reaction. While the pyrogenic reaction is of itself not dangerous, the added load it imposes upon patients already critically ill cannot be disregarded.

Pyrogenic reactions are caused, almost invariably, by the inadvertent injection of foreign protein matter with the blood. Such foreign material may be present in any part of the transfusion apparatus, and particularly in the rubber tubing. A frequent source of febrile reaction is the water from which

the solutions are made, or that which is used for the final irrigation of the apparatus.[11] If, in the process of distillation, such fluids are incompletely freed from pyrogenic material, febrile reactions will ensue. Similar reactions are frequently seen following infusions of saline or glucose solutions which contain protein contaminants. In evaluating the source of posttransfusion reactions, therefore, it is important to know whether such fluids, if given, contained pyrogenic substances.

Allergic reactions following transfusions of blood usually manifest themselves in the form of urticaria, occasionally by asthma or other visceral disturbances. Such reactions are readily controlled, as a rule, by the administration of adrenalin and are included, therefore, with the minor reactions. They are seen at times when a patient receives blood from the same donor for a second or third time, or when the donor has a history of allergic sensitivity. Occasionally, such reactions can be traced to blood drawn shortly after the donor has eaten. To reduce the incidence of this type of reaction, it would appear that allergic persons should not be taken as blood donors and that, whenever possible, blood should be drawn during the fasting state. However, allergic symptoms are frequently seen following transfusions where neither the patient nor donor have been known to have allergic tendencies.

Hemolytic reactions are extremely uncommon, fortunately, since the general adoption of careful and accurate blood typing and cross-matching. Such reactions are usually due to incompatibility of the bloods, although occasionally overheating or prolonged storage of blood may cause sufficient destruction of red cells to cause a hemolytic reaction. The clinical manifestations of such reactions are severe lumbar pain, dyspnea, cough, chills, and varying degrees of collapse, followed by jaundice and hemoglobinuria. These may lead to complete anuria and death from uremia. If diuresis can be effected, recovery usually ensues. The severity of hemolytic reactions is proportional to the amount of erythrocytic destruction in the infused blood.

Analysis of Records of 2,500 Transfusions.—In order to determine the actual incidence of blood transfusion reactions, and to compare the incidence following successive changes in technic, we have studied five series of 500 transfusions each. Prior to 1937, direct transfusions were administered routinely at the hospital. The technic used was the Strauss[12] modification of the Lindeman method, in which multiple large syringes are alternately filled with blood from the donor and immediately discharged into the vein of the recipient. The first series consists of 500 consecutive transfusions done by this method.

During the year 1937, citrate transfusions were reintroduced into the hospital and, almost overnight, there was a general and spontaneous adoption of this method. The original Lewisohn technic was employed, wherein the blood is collected into an open flask or beaker containing citrate solution, and is infused by gravity through a funnel, with several thicknesses of gauze for a filter. The second series of transfusions was drawn from this period.

The third series of cases dates from 1939, and represents the early experi-

ences with the revised technic in the new Transfusion Department. The fourth series of 500 transfusions were taken from the second year of the activities of the Transfusion Center after the elimination, one by one, of a number of sources of transfusion reactions. The final series of 500 transfusions were given during a ten-week period in the spring of 1941, and represent the current status of transfusion effects.

RESULTS.—The change in transfusion technic from the direct to the citrate blood method was reflected in an immediate and striking increase in the number of transfusions given. Prior to 1937, an average of 500 transfusions were given annually in the hospital. At the present time, thanks to the greater ease and facility of the citrate method, the number has risen to 2,500 transfusions per year. The cases studied in this report obviously do not represent all of the transfusions given during the period covered, but are sample batches of unselected, consecutive series numbering 500 each, drawn during successive stages in the evolution of our present transfusion program.

Incidence of Reactions.—Our investigations indicate a progressive reduction in the incidence of blood transfusion reactions in the five successive series of transfusions studied (Table I). The direct transfusions gave a surprisingly high incidence of reactions, when subjected to actual statistical analysis. Febrile reactions contributed the greatest number. They were noted in 7.7 per cent of the transfusions, and in 5 per cent they were of major severity. In retrospect, this high incidence of pyrogenic reactions is not surprising. The importance of the utmost care in eliminating foreign material from all equipment and solutions was not thoroughly appreciated. The syringes and tubing were not given the special attention now considered essential in preparing transfusion equipment. During the transfusion, the syringes were rinsed in open basins containing citrate solution, distilled water and salt solution, the manufacture of which was done in a routine manner. It is a tribute to the method, which permitted but limited contact of blood with foreign surfaces, that the incidence of reactions was not higher.

Series II, comprising a sample of 500 consecutive citrated blood transfusions done by the open method showed, surprisingly, a slightly lower incidence of reactions than did the direct method. In this group there were a total of 7.4 per cent reactions, with pyrogenic disturbances in 7 per cent. Of these, 6 per cent were classed as major reactions. The manifold potential sources of contamination with pyrogen-containing substances are obvious. Nevertheless, there was probably less contact of the equipment with impure solutions, which is reflected in the slightly lower incidence of febrile reactions.

The third series of transfusions comprised the first 500 given under the present set-up. The results were somewhat disappointing. Although there was some reduction in the number of reactions, this was not as striking as had been expected. The total reaction rate was 7.2 per cent, of which 5.2 per cent were pyrogenic and, of these, 3.8 per cent were of major severity. However, the system of adequate record keeping, and the use of the pyrogen test to detect the source of contamination, permitted a progressive elimination of

the various factors responsible for reaction, with gradually diminishing incidence of untoward effects.

The importance of these measures is demonstrated by the figures presented by Series IV. A striking fall in the incidence of pyrogenic reactions is seen, to 2.8 per cent, of which only 1.6 per cent are classed as major reactions. This represents a reduction to approximately 50 per cent of the previous series. The last series, indicative of our present rate of reactions, is encouraging indeed. The total number of reactions amounted to slightly over 2 per cent, with only 0.6 per cent of major pyrogenic disturbances. With continued alertness and further improvements in technic, even better results are to be anticipated.

TABLE I

INCIDENCE OF REACTIONS FOLLOWING TRANSFUSIONS

	Pyrogenic Reactions			Allergic Reactions	Hemolytic Reactions	Total Reactions
	Major	Minor	Total			
Series I						
500 Consecutive Direct Transfusions (multiple syringe) 1936	25 (5.0%)	14 (2.8%)	39 (7.8%)	9 (1.8%)	0	48 (9.6%)
Series II						
500 Consecutive Indirect Transfusions (open method) 1938	30 (6.0%)	5 (1.0%)	35 (7.0%)	2 (0.4%)	0	37 (7.4%)
Series III						
500 Consecutive Indirect Transfusions (early new method) 1939	19 (3.8%)	7 (1.4%)	26 (5.2%)	10 (2.0%)	0	36 (7.2%)
Series IV						
500 Consecutive Indirect Transfusions (recent new method) 1940	8 (1.6%)	6 (1.2%)	14 (2.8%)	5 (1.0%)	0	19 (3.8%)
Series V						
500 Consecutive Indirect Transfusions (Feb. to May, 1941)	3 (0.6%)	8 (1.6%)	11 (2.2%)	4 (0.8%)	0	15 (3.0%)

In all of the cases presented here, the blood transfusions were charged with a certain number of reactions for which they were not really responsible. Most patients who are ill enough to require blood transfusions also receive infusions of salt and glucose solutions. As has been indicated, such infusion liquids are as capable of inducing febrile reactions as are blood transfusions, if pyrogenic contaminants are present. Recently, commercial infusion liquids have been adopted for routine use in the hospital, and the preparation of the tubing and needles has been subjected to the same care and supervision as is employed with transfusion equipment. This should be reflected, not only in a lower incidence of infusion reactions, but also in the number of reactions attributed to blood transfusions.

In an attempt to further analyze the causes of transfusion reactions, these were correlated with the diseases for which the transfusion was administered. In a study of 1,000 consecutive transfusions, (Table II) pyrogenic reactions were encountered most frequently in patients suffering from various types of blood dyscrasias, including leukemias, thrombocytopenic purpuras, hemolytic anemias, *etc.* This observation has been made by others.[8] Furthermore,

pyrogenic reactions were more frequently seen in febrile than in afebrile patients. It appears that patients suffering from septic diseases are particularly sensitive and responsive to minute and otherwise innocuous amounts of pyrogenic material. In these patients, chill reactions could be reduced in frequency and severity by the administration of multiple small transfusions, not exceeding 250 cc. of blood at a time. This presumably reduces the quantity of pyrogenic substance sufficiently to prevent reaction even in a sensitive patient.

This predisposition on the parts of septic patients to sustain reactions may explain, in part, the higher incidence of reactions on the medical services than on the surgical services. Within the surgical group, pyrogenic reactions occurred more frequently in patients treated for gynecologic disorders than in any others. In 29 patients of the "clean" Orthopedic Service, who were transfused during or after orthopedic operations, not a single untoward reaction occurred. The series, however, is too small to warrant drawing definite conclusions.

TABLE II

THE INCIDENCE OF TRANSFUSION REACTIONS IN PATIENTS CLASSIFIED ACCORDING TO DIAGNOSIS AND DEPARTMENT

	No. of Transfusions	Pyrogenic Reactions	Per Cent	Allergic Reactions	Per Cent	Total Reactions	Per Cent
Surgical Patients							
Gynec. surgery	56	4	7.1	1	1.8	5	8.9
Orthoped. surgery	29	0	0.0	0	0.0	0	0.0
All other surg. depts.	415	10	2.4	3	0.7	13	3.1
Medical Patients							
Blood dyscrasias	45	8	17.7	0	0.0	8	17.7
Ulcerative colitis	50	1	2.0	5	10.0	6	12.0
All other medical diseases	340	13	3.8	5	1.4	18	5.2
Obstetrics	65	4	6.1	1	1.5	5	7.6
Totals	1,000	40	4.0	15	1.5	55	5.5

An interesting finding was the fact that reactions seemed to occur in aggregates of four or five within a day or two, followed by no reactions for perhaps two or three weeks. Invariably, we were able to trace the causes for these reactions and, in most cases, to remedy the cause. On one occasion, it was a batch of new tubing that had been inadequately prepared. Another time the salt solution contained pyrogenic impurities, and in a recent occurrence of chill reactions, it was found that particles of old blood were left behind because the metal valves were not taken apart in the course of cleansing. The important point is that, by virtue of the accurate record system, it was relatively easy to trace the various sources of contamination.

It will be noted from the tables that no hemolytic reactions were encountered in the entire series of transfusions reported. Freedom from this, the most dangerous type of posttransfusion reaction, is attributed to the carefulness of the preliminary typing and compatibility tests. By using only high-titer testing sera and by rejecting all bloods giving a questionable agglutination, the dangers of subgroup agglutinations can be avoided. Reciprocal

cross-matching of both serum and cells of recipient and donor further protects the patient from receiving incompatible blood.

The Use of Universal Donors.—Several investigators[6, 10, 13] have shown that infusion of blood from universal donors (Group O) into patients of other blood groups may result in hemolytic reactions. The use of universal donor-blood is considered especially dangerous if the agglutinin titer of the donor's serum against the recipient's cells is 1:32 or higher, and if more than 200 cc. of blood of this type is used.

In our series of 1,000 recent transfusions studied, universal donor-blood was given to patients of other blood groups 220 times. The percentage of untoward reactions was actually lower in these cases than in the other 780 in which recipient and donor belonged to the same blood group. According to Wiener[13] such statistics have not been previously recorded. No hemolytic reactions were encountered, regardless of the agglutinin titer of the donor's serum. In most instances, 500 cc. of blood was given. We believe, therefore, that it is safe to administer universal donor-blood to patients of other blood groups, provided, by the use of high-titer typing sera, the correct group classification of the donor is assured. Careful direct compatibility tests between recipients' and donors' bloods must be performed before every transfusion to rule out the presence of anti-O agglutinins in the recipients' serum.[14] The same principles should apply to the transfusion of other blood group bloods to universal recipients.

TABLE III

INCIDENCE OF REACTIONS IN PATIENTS TRANSFUSED WITH BLOOD OF THE SAME TYPE AND IN THOSE RECEIVING BLOOD OF A DIFFERENT TYPE (UNIVERSAL DONOR-BLOOD)

	Number of Transfusions	Pyrogenic Reactions	Allergic Reactions	Total Reactions
Patients and donors of same blood group.....	780	35 (4.5%)	12 (1.5%)	47 (6.0%)
Patients and donors of different blood group...	220	5 (2.2%)	3 (1.4%)	8 (3.6%)
Totals.....	1,000	40 (4.0%)	15 (1.5%)	55 (5.5%)

SUMMARY AND CONCLUSIONS

(1) The control of blood transfusion reactions demands centralized responsibility over all of the component steps of the operation, careful supervision of the numerous potential sources of error, and everlasting alertness to trace and eliminate factors causing untoward reactions.

(2) The organization of a Blood Transfusion Department for a general hospital is described.

(3) Five series of 500 transfusions each are analyzed, tracing the gradual reduction in the incidence of transfusion reactions as the various causative factors are successively eliminated.

(4) The importance of detailed records is emphasized. Complete data covering all phases preliminary to and following every transfusion make it possible to trace and eliminate the causes of reactions when they occur.

(5) The pyrogen test is an effective aid in controlling the preparation of the solutions and equipment.

(6) Reactions following transfusions are classified as pyrogenic, allergic, and hemolytic.

(7) Pyrogenic reactions constitute the largest number of posttransfusion reactions. They are characterized by fever with or without chills. They are almost invariably due to the presence of foreign contaminants in the solutions or apparatus. Sepsis and blood dyscrasias predispose to pyrogenic reactions.

(8) Allergic reactions are usually urticarial in nature. The chief causes are donors with allergic tendencies and donors who have eaten shortly before giving blood. Patients with ulcerative colitis seemed to be predisposed to allergic reactions.

(9) Hemolytic reactions are usually due to the administration of incompatible blood. This can be avoided only by careful preliminary typings and reciprocal cross-matchings, the use of high-titer testing sera, and the rejection of all bloods giving questionable agglutinations. There were no hemolytic reactions in our series.

(10) Universal donor-blood gave no higher incidence of reactions than did blood of homologous groups.

(11) Our statistics reveal a reduction in the reaction incidence from 9.6 to 2.2 per cent. Only 0.6 per cent of the latter figure were major pyrogenic reactions. Our experiences point the way to the reduction of transfusion reactions, and give promise that continued improvement is to be anticipated.

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THE TREATMENT OF CERVICAL METASTATIC CANCER

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THE TREATMENT of cervical metastases is a problem which confronts every surgeon and radiologist who deals with intra-oral and pharyngeal cancer. Since the results of all methods of treatment fall so far short of a complete solution, the question of treatment must be approached open-mindedly, in its broadest aspects. In order to discuss this problem intelligently, one must first know what is meant by the term "cervical metastases." For this purpose, a few years ago, 500 consecutive cases of cervical metastases were tabulated at the Memorial Hospital according to the site of the primary lesions. These data were not taken from the clinical records but were tabulated at the time the metastases were first noted, either when the patients were admitted to the clinic or when the involved nodes were discovered at a later examination. This particular study was made only to determine the distribution of the primary sites and was not used in any of the other calculations given in this paper. The statistics are given in Table I.

TABLE I

LOCATION OF PRIMARY LESION IN 500 CONSECUTIVE CASES

Tongue	127 (25%)
Floor of mouth	44 (9%)
Extrinsic larynx	44 (9%)
Nasopharynx	40 (8%)
Lip	35 (7%)
Tonsil	34 (7%)
Mucosa of cheek	28 (6%)
Metastatic from undetermined primary	28 (6%)
Jaws	27 (5%)
Pharyngeal wall	24 (5%)
Palate	20 (4%)
Skin of face	11 (2%)
Thyroid	11 (2%)
Miscellaneous	27 (5%)
	500(100%)

Table I demonstrates that no single anatomic variety of intra-oral or pharyngeal cancer can be taken as representative of all cervical metastasis. It will be noted that cancer of the tongue causes 25 per cent (one in four) of all cervical metastases, and that cancer of the lip, upon which the majority of published reports concerning cervical metastases have been based, produces only one in about 15 cases, sharing only fifth place with cancer of the tonsil. A broad view of the problem of cervical metastasis, therefore, necessitates a consideration of all forms of intra-oral and pharyngeal cancer in all stages of the disease.

There is wide divergence of opinion as to the best methods of treatment for cervical metastatic cancer. Surgery and radiation both have their exponents, while some radiologists and surgeons of considerable experience doubt the

possibility of cure by any method. It is my purpose in this report to present evidence that no single treatment method is indicated exclusively; that both surgery and radiation have definite fields in the treatment of cervical metastases; and that in a considerable number of cases a combination of the two is better than either used alone. It would simplify the discussion of this proposition if the method of treatment could be selected according to a set formula, depending only upon the anatomic characteristics of the involved nodes themselves. Unfortunately, this is not possible. There are several factors relating to the primary lesion which are also of importance in the determination of the proper treatment of metastases. Although closely related, the management of the primary lesion and of the cervical metastases should be considered as separate problems, dealt with in most cases by separate procedures. I shall base my discussion on that premise, omitting any reference to the treatment of the primary lesion except as it affects the treatment of the metastases.

From the practical standpoint, the problem may be considered under two headings: (1) Prophylactic treatment, or that which is given in the absence of clinically demonstrable metastases; and (2) curative treatment given for clinically positive metastases.

Prophylactic Treatment.—At the Memorial Hospital it has been the policy for the past several years to apply no prophylactic treatment of any kind to the neck in intra-oral cancer. The patients are reexamined at regular intervals, and only if and when metastases become clinically demonstrable is treatment given, and then with curative intent. The logic of such a conservative plan is based upon a statistical analysis of the subsequent clinical behavior and the eventual results in those patients who applied without cervical metastases and who were treated according to this plan.

Even though prophylactic treatment were highly efficient in dealing with clinically undemonstrable cervical metastases, nevertheless the justification for its routine use would depend also upon the percentage of cases in which it could be of actual value. It must be admitted that prophylactic treatment could be of ultimate value only in patients who apply without clinically demonstrable nodes, whose primary lesions are permanently controlled, and who then later develop cervical metastases. In other words, prophylactic treatment would be futile if the patient succumbed to an uncontrolled primary lesion or if he never developed cervical metastases in his untreated neck.

The hypothetic limit of the value of prophylactic neck dissection in cancers of the lip, cheek, and tongue is shown in Table II. Of 128 consecutive determinate cases of cancer of the lip without metastases on admission, in which the primary lesions were controlled for at least five years, only four patients (3 per cent) later developed metastases. In this group, therefore, prophylactic neck dissection could not have had even a theoretic value in 125, or 97.5 per cent, whereas under the higher reported mortality rates following neck dissection, over 10 per cent of the patients would have died of postoperative complications, about four times the number which the procedure could possibly have cured. In any case, even under the lower reported mortality rates, would

it have been worth while to perform 128 neck dissections in order to anticipate metastases in three patients, when as a matter of fact these three were all cured by subsequent treatment? There is a similar trend in cancer of the tongue and of the cheek. If one accepts the proposition that prophylactic neck

TABLE II

HYPOTHETIC LIMIT OF THE VALUE OF PROPHYLACTIC NECK DISSECTION

Prophylactic treatment to the neck could have been of actual value only in those cases admitted without palpable metastases, in which the primary lesion was, eventually, permanently controlled and in which clinically demonstrable metastases appeared at a later date

	Patients Admitted Without Palpable Cervical Metastases in whom the Primary was Permanently Controlled	Patients who Later Developed Cervical Metastases
Cancer of tongue (1931–1934).....	40	5 (12%)
Cancer of lip (1928–1932).....	128	4 (3%)
Cancer of cheek (1930–1934).....	12	2 (17%)

dissection can be of value only when the primary lesions remain cured and when metastases would eventually appear, then only about one in 33 prophylactic neck dissections in cancer of the lip can be of value, one in six in cancer of the cheek, and one in eight in cancer of the tongue.

In the case of radiation, prophylactic treatment as ordinarily given (one to two skin erythema doses to each side of the neck) does not carry with it any mortality, but if it cannot be demonstrated that such radiation is beneficial, then it must be conceded that it is at least wasteful from an economic standpoint even though otherwise harmless. Since such small dosage has never been observed (or at least reported) to sterilize a proven focus of epidermoid carcinoma, why should it be assumed capable of sterilizing an impalpable focus (the actual existence of which cannot be proved) simply because the patient survives and does not subsequently develop metastases?

In the final analysis, it seems to me that the evidence, both theoretic and statistical, fails to provide any justification for prophylactic treatment in intraoral and pharyngeal cancer. On this basis, treatment is administered only if and when cervical nodes are clinically involved.

Choice of Treatment Methods for Clinically Positive Cervical Metastases.—The selection of the particular form of treatment for clinically demonstrable cervical metastases should be based upon the clinical features of the given case rather than on any partisan preference for one or another method. The special indications for radiation and for surgery in cervical metastatic cancer differ widely. It is fortunate for surgery that radioresistance is often associated with the more slowly developing, orderly metastasizing, and less malignant forms of cancer. It is equally fortunate for radiation therapy that the more malignant, rapidly and widely metastasizing lesions not suitable to surgery tend to be among the more radiosensitive. The clinical behavior of a given case of intraoral or pharyngeal cancer may be predicted with a fair degree of accuracy from the site of the primary lesion and from the histologic type of the growth.

For instance, cancer of the lip is usually squamous carcinoma Grades I or II. The rate of growth is moderate, metastases develop relatively late in the course of the disease, in an orderly manner, and often after permanent control of the primary lesion. For such cases, neck dissection is suitable.

At the other extreme are the highly malignant, rapidly progressing anaplastic growths of the base of the tongue or of the nasopharynx which metastasize early, bilaterally, and widely throughout the neck. While these cases are unsuited to surgery, both because of the location of the primary lesion and because of the histologic character and distribution of the cervical nodes, nevertheless these growths are highly radiosensitive and respond favorably to radiation treatment.

In assaying the relative values of radiation and surgery for cervical metastases, one must admit that each has its own limitations and disadvantages. Little is gained by an attempt to prove the superiority of one method over the other. The two need never be considered as competitive, but rather as complementary, and the selection of the exact treatment procedure in the individual case depends on the experience and ability of the surgeon. An outline of the conditions influencing the selection of treatment methods for cervical metastases is given in Table III.

TABLE III

CONDITIONS INFLUENCING SELECTION OF TREATMENT METHOD IN CERVICAL METASTATIC CANCER

Favorable to Surgery	Metastases Clinically Evident	Favorable to Radiation
(1) Primary controlled		(1) Primary uncontrolled or under treatment
(2) Nodes operable		(2) Nodes inoperable
(3) Metastases unilateral		(3) Metastases bilateral
(4) Radioresistant, histologically differentiated tumors		(4) Radiosensitive, anaplastic tumors
(5) Primary lesions of lip, mucosa of cheek, anterior tongue, floor of mouth or gums		(5) Primary lesions of base of tongue, tonsil, nasopharynx, extrinsic larynx, pharyngeal walls

A combination of radiation and surgery is usually the best solution when an individual case fails to conform in more than one respect to either set of conditions.

Treatment by Radiation.—When all primary sites are considered, radiation is undoubtedly more useful—that is, applicable in more cases—than surgery for the treatment of cervical metastases. A combination of protracted fractional x-radiation through narrow skin portals limited to the area immediately adjacent to the node and supplementary implantation of radon gold seeds has proved to be the most efficacious radiation method in the Head and Neck Clinic at the Memorial Hospital. The essential factors in this radiation technic are: First, to deliver a cancer lethal dose to the immediate vicinity of the metastatic nodes with as little damage as possible to the surrounding normal tissues; and, second, to conserve the general tolerance of the patient. The greatest avoidable cause of failure of radiation therapy in any part of the body is the irradiation of unnecessarily large volumes of tissue, so that even though the growth may be destroyed, the patient cannot survive the effects of the treatment.

Aspiration biopsy of at least one involved node should be made in each patient treated by radiation. Such confirmation of the diagnosis is essential for purposes of record. When a node is clinically involved, radiation treatment if otherwise intended should not be withheld or even delayed because of the failure to obtain a positive aspiration biopsy, but the accuracy of the surgeon's clinical diagnosis will be improved if he subjects himself to the discipline of an attempt at histologic confirmation in all cases, and if he limits his claimed cures to those cases which have been so proved.

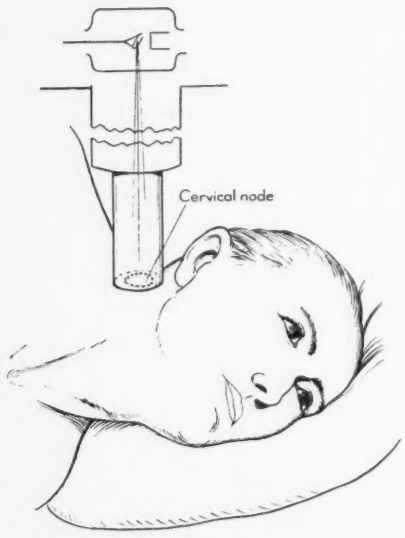

FIG. 1.—External radiation of a single cervical node. In order to deliver a cancer-lethal dose of x-radiation to a single cervical node, the beam must be small and directed to the immediate vicinity of the node itself rather than to the entire lymph-node-bearing area of the neck. Limitation in size and accurate positioning of the skin portal are favored by the use of metal cylinders in direct contact with the skin.

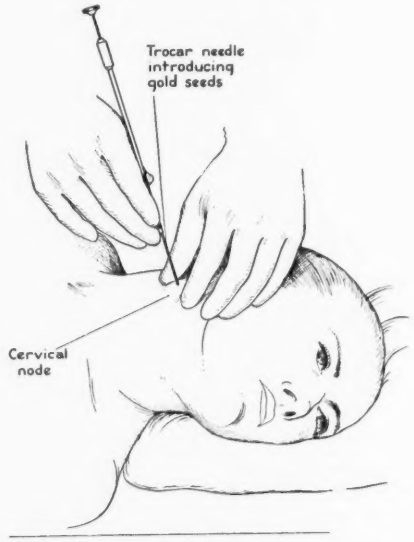

FIG. 2.—Implantation of radon seeds through the skin. Radon gold seeds may be implanted into a cervical node or into a subcutaneous mass through puncture wounds in the skin—a convenient and time-saving method if the node is not situated under too deep a layer of subcutaneous fat.

Fractionated X-Radiation.—To localize the external radiation, circular portals are used, limited in size so as to include only the node and a margin of 1–1.5 cm. (Fig. 1). In the average case, for the treatment of individual nodes such portals will vary between 3 and 5 cm. in diameter (the smallest 2.5 cm.). Separate portals are used for widely separate nodes. Immediately adjacent nodes are treated as single masses. Depending upon the size of the portal a total of 4,000–8,000 r. or even more is given by daily divided doses over a period of two to three weeks. Immediately on the completion of this external dose, radon seeds in a tissue dose of five to ten S.E.D. (skin erythema doses) are implanted either through a puncture wound in the skin (Fig. 2), or after surgical exposure of the outer surface of the node.

Surgical exposure is indicated when the node lies deeply under a thick layer of subcutaneous fat, where the accurate placement through skin punc-

tures is not possible by palpation alone. In these cases, it is advisable to anticipate the radiation skin reaction by performing the surgical exposure at the end of about two weeks of x-radiation.

Such a plan of localized irradiation of individual nodes, based upon the principle of treating cancer only when and where it is at least clinically present, makes it possible to treat several separate involved nodes in the same case. One of the difficulties in the way of the general acceptance of this plan of treatment by surgeons is that it contravenes an accepted principle which is entirely reasonable when applied to surgery alone; namely, that in neck dissection the entire mass of lymph node bearing tissues of one side of the neck should be removed. In radiation therapy the opposite holds true—radiation of the entire neck in cancer lethal doses is dangerous, and far better results will be obtained by local and individual treatment of each separate involved node.

Interstitial Radiation.—When radium emanation is available, there can be little question but that radon gold seeds are the most useful form of interstitial applicator for supplementing fractionated x-radiation. In the small nodes, the supplementary seeds in a single tissue dose of five to six S.E.D. are implanted after about two to three weeks of fractionated x-radiation. In the larger more resistant masses the dose of radon seeds is also fractionated, and the series of external treatments is interrupted at about seven- to ten-day intervals, and two or even three fractions of radon seeds are given. In the more difficult cases the total doses of both x-radiation and seeds should approach the local and general tolerance. The dosage in such cases is empiric and so variable as to be learned only by experience. Radon seeds alone are sometimes satisfactory for small or moderate-sized nodes up to 1.5 cm. in diameter.

Treatment by Surgery.—The only justifiable surgical method for the treatment of cervical metastases is neck dissection, which implies the complete removal in a given area of all lymph-node-bearing tissues between the superficial subcutaneous fat and the fascia covering the deep muscles of the neck. The extent of such an operation may vary from a local dissection of the submental and submaxillary triangles to a complete or block dissection extending from the lower edge of the mandible and the mastoid to the clavicle, and from the anterior border of the trapezius forward to the midline. A form of incision, usually a variation of the crucial or the trifurcate, should be selected which will permit adequate exposure of the operative field. Details of block neck dissection as performed in the clinic at the Memorial Hospital are given in Figures 3–6, inclusive.

Local is preferable to general anesthesia. The highest mortality rates are usually reported from those clinics where general anesthesia is used routinely. At the Memorial Hospital, in 210 neck dissections performed on the Head and Neck Service over a ten-year period from 1930–1939, inclusive, there were five postoperative deaths, a mortality of 2.4 per cent in the whole group (Table IV). In 196 operations performed under local anesthesia, there were only three deaths, a mortality of only 1.5 per cent. Two of the deaths occurred

in the 14 operations performed under general anesthesia, a mortality of 14.3 per cent. In extenuation of the higher mortality in the latter group, it should be stated that general anesthesia was used only for the most difficult and complicated situations where the nature of the procedure would have rendered

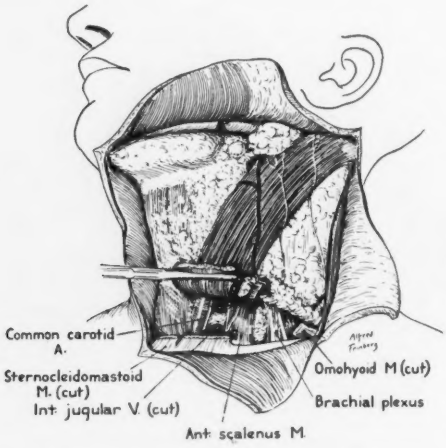

FIG. 3.—A form of incision is selected (trifurcate, crucial, or a modification) which will permit of adequate exposure of the operative area. The skin flaps are dissected back. A complete or block dissection begins at the clavicle where the sternomastoid muscle, the internal jugular vein and the omohyoid muscle are cut across.

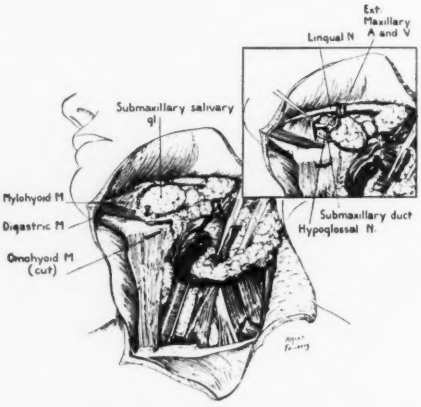

FIG. 4.—The limits of a complete unilateral block dissection are the midline anteriorly, the border of the trapezius muscle posteriorly, the clavicle below, and the submental space and the lower border of the mandible superiorly. The deep level of the dissection is the fascia overlying the pretracheal and lateral cervical muscles. The common carotid artery, the vagus and the phrenic nerves, and the origin of the brachial plexus are exposed. The submaxillary salivary gland and the contents of the submaxillary triangle are removed down to the level of the mylohyoid and hyoglossus muscles. The sensory branches of the cervical plexus are excised. The accessory nerve is sacrificed.

local anesthesia inadequate. At the present time, it is rarely necessary to employ the more dangerous general anesthesia for this operation.

TABLE IV

NECK DISSECTIONS FOR CERVICAL METASTATIC CANCER

January 1, 1930 to December 31, 1939

Total Neck Dissections		210
Local anesthesia		196
Postoperative deaths		3
Postoperative mortality	1.5%	
General anesthesia		14
Postoperative deaths		2
Postoperative mortality	14.3%	
Total postoperative mortality	5 cases	2.4%

Treatment by Combinations of Radiation and Surgery.—The value of preoperative and postoperative radiation in small doses is often brought up for discussion. Until about 1930 it was a common practice in all cancer clinics to apply small doses (one to two S.E.D.) of radiation to the operative field either immediately before or immediately after practically all operations for cancer (neck, breast, pelvis, extremities, *etc.*). The theory for giving preoperative radiation was that the malignancy of the tumor and its tendency

toward dissemination during the operation would thereby be reduced. The theory for giving postoperative radiation was that if any cancer cells had been missed or had been spilled into the operative wound, these small doses of radiation would destroy them so that subsequent recurrence would not take place. From what is now known of cancer-lethal radiation dosage, one

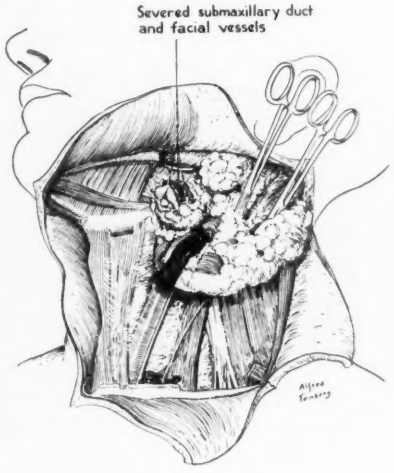

FIG. 5.—In order to remove the submaxillary salivary gland, the submaxillary duct and the facial vessels are cut and ligated.

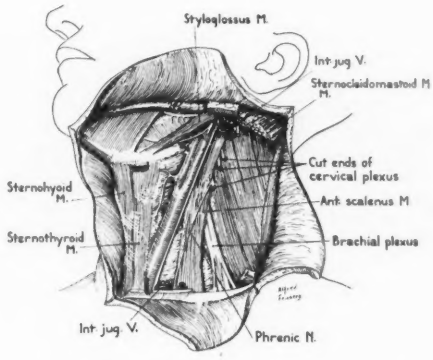

FIG. 6.—The dissecuon is completed by cutting across the tip of the parotid gland and across the upper portion of the sternomastoid muscle. Great care is taken to remove completely the subdigastric lymph nodes which lie just below and under the inferior edge of the posterior belly of the digastric. At this point, the internal jugular vein is ligated and cut across.

to two S.E.D. will not sterilize epidermoid or adenocarcinoma, and in my opinion there is no sound evidence that it can produce even a deterrent effect which will in any way modify the pre- or postoperative course. The attempts to apply cancer lethal doses pre- or postoperatively usually result in rather tragic failures of wound healing.

I mention such pre- and postoperative radiation measures only to point out that I do not include them under the definitely worth while and effective combinations of radiation and surgery which will be discussed in the following paragraphs.

Combinations of Surgery and Heavy Radiation.—The conditions under which effective combinations of surgery and radiation are useful can best be illustrated by citing examples. Metastatic nodes from cancer of the tongue, cheek, or lip are sometimes infected and centrally necrotic with perforation of the node capsule and invasion of the adjacent tissues. With surgery alone the possibility of complete removal of such nodes is rather remote. With radon alone, a lethal dose to the entire volume of the necrotic node will invariably bring on a further breakdown of the tissues and a discharging sinus which is slow to heal. Such patients may often be successfully treated by applying a dose of radiation (radon seeds alone or combined with external radiation),

following which the height of the radiation reaction is anticipated by surgically excising the condemned mass of tissue.

The two methods may also be effectively combined during neck dissection when a metastatic node, thought to be operable, is found to infiltrate beyond its capsule into a structure which cannot be widely excised. In such a case, a small remnant of the tumor, 1–1.5 cm. in diameter, may be left and a heavy dose of radon seeds inserted immediately, the remainder of the neck dissection proceeding as usual. At the Memorial Hospital, it is a routine practice to have radon gold seeds available for such a contingency in all neck dissections.

Prognosis.—The prognosis in cervical metastatic cancer is by no means hopeless, despite the rather discouraging opinions sometimes expressed by both surgeons and radiologists. The chance of cure is best in those patients who develop metastases late in the course of the disease, especially after control of the primary lesion (Table V). It is worst in those who already have metastases at the time of their first examination. The chance of cure in the bilaterally metastasizing, highly anaplastic tumors, such as cancer of the nasopharynx, hopeless heretofore by surgical treatment alone, has been so much improved by the advent of modern radiation therapy as to approach the results by surgery in the highly differentiated radioresistant and slowly metastasizing tumors such as cancer of the lip. The cure rates shown in Table V are calculated on consecutive cases of patients in all stages of the disease treated by radiation or surgery or combinations of the two. From these statistics, it is apparent that the capacity to metastasize and the presence of metastases at some time during the course of the disease are the most significant factors in the prognosis of any form of cancer.

TABLE V

THE INFLUENCE OF METASTASES ON THE PROGNOSIS OF INTRA-ORAL AND PHARYNGEAL CANCER

Site of Primary Growth	Total No. of Cases	Five-Year Cure Rate: With Metastases %	Five-Year Cure Rate: Without Metastases %	All Cases Percentage
Lip	313	27	95	70
Cheek	78	21	30	27
Tongue	208	12	45	25
Floor of mouth	87	22	29	25
Gingiva	85	8	42	24
Palate	57	6	54	21
Tonsil	148	10	38	18
Nasopharynx	80	20	47	25

ILLUSTRATIVE CASE REPORTS OF CERVICAL METASTASES FROM INTRA-ORAL CANCER

Case 1.—Cancer of the Tongue: J. A., male, age 67, admitted November, 1932, complaining of sore on tongue of two months' duration, which had gradually increased in size. The patient gave a history of having been a heavy cigar smoker until six months before admission. The Wassermann was negative. The lesion, 2 cm. in diameter, raised and partly ulcerated, was located on the left side of the dorsum of the tongue, 2.5 cm.

back from the tip. The biopsy showed squamous carcinoma Grade II. There was no palpable adenopathy.

After implantation of 15 mc. of radon gold seeds, the lesion regressed and the patient remained well until March, 1933, when an enlarged node, 2.5 cm. in diameter, appeared over the left upper, deep cervical region. An aspiration biopsy was positive for metastatic cancer. In April, 1933, the outer surface of the node was surgically exposed, and 27 mc. of radon gold seeds were implanted. After healing, a scarred, indurated mass remained in this region, but the patient has been otherwise free of disease for seven years.

Case 2.—Cancer of the Floor of the Mouth: J. C., male, age 67, admitted November, 1932, complaining of soreness in the floor of the mouth of one year's duration. He had been treated by his family physician with repeated applications of silver nitrate. Three weeks before admission, following severe pain, the patient examined his mouth and found an ulcer. He gave a history of having smoked a pipe excessively for years. The Wassermann was negative. The lesion was located in the midline of the floor of the mouth, partly ulcerated, indurated, 2 cm. in diameter and infiltrating to a depth of about 1 cm. The biopsy showed squamous carcinoma Grade II. There was no cervical adenopathy.

Treatment was given by roentgenotherapy through portals, 5 cm. in diameter, one directed to the submental region and one to each side of the chin, for a total dose of 2,400 r. x 3. There was apparent complete regression, but residual disease was proved by biopsy three months later, and 8 mc. in radon gold seeds were implanted. This treatment was followed by localized radium necrosis which did not heal entirely for one year.

In July, 1933, enlarged nodes appeared over both submaxillary regions, overlying the submaxillary salivary glands. Aspiration biopsy of the node on the right was diagnosed as metastatic cancer. Radon seeds were implanted in both submaxillary nodes through the skin, 26 mc. on the left and 10 mc. on the right. The patient remained well until October, 1935, when a biopsy from a suspicious area in the floor of the mouth was positive. The recurrence was treated by actual cautery in November and again in December, 1935. Since that time the patient has remained free of disease—in the neck since 1933, and in the floor of the mouth since 1935.

Case 3.—Cancer of the Tongue: H. R., male, age 58, admitted in June, 1936, with an ulcer on the tongue of two months' duration, accompanied by some pain. The patient gave a history of white spots on the lips and tongue for 25–30 years, and stated that he smoked five to six cigars daily. The Wassermann was positive. The lesion, centered 4 cm. back from the tip of the tongue, was 3 cm. in diameter, infiltrating to a depth of 1 cm. The biopsy showed squamous carcinoma Grade II. There were no palpably enlarged lymph nodes.

The lesion was treated with peroral x-radiation (3,500 r., cone 4 cm., T.S.D. 65 cm.) and 8 mc. of radon gold seeds. In September, 1936, an enlarged node appeared over the right submaxillary salivary gland. An aspiration biopsy showed squamous carcinoma. The node was treated with 5,500 r. through a 4 cm. portal. It became fluctuant and was obviously liquefying. In October, 1936, a neck dissection was performed. The node was found to be an abscess about 4 cm. in diameter on the mesial aspect, infiltrating the mylohyoid and hyoglossus muscles; the latter area was not considered surgically removable since it extended into the tongue. Twenty-six millicuries of radon gold seeds were implanted into the residuum which could not be removed, and the neck dissection proceeded as usual. The patient has remained well for three and one-half years. A lesion on the lip which was a papilloma and leukoplakia only was treated by radiation and regressed completely.

End-Results.—It is difficult to gather any very definite data from the medical literature concerning the actual cure rate in cervical metastatic cancer. A few pessimistic surgeons and radiologists report that they have never ob-

tained cures once intra-oral or pharyngeal cancer has spread to the neck. Most investigators, however, report cures, but the statistics, for the most part, are based upon series of neck dissections for lip cancer only and have, therefore, only a limited significance in regard to the whole problem, since cancer of the lip is the most easily cured of all forms of intra-oral cancer, both at the primary site and in the cervical nodes. Some of these authors have not separated the cases with histologically positive nodes from those with negative nodes, and the actual cure rate for metastatic cancer is, therefore, obscured.

TABLE VI

NECK DISSECTIONS FOR CANCER—JANUARY 1, 1930 TO APRIL 1, 1934

Successful Results in Cases with Histologically Positive Nodes

	Total No. of Cases	Five-Year Survivals	Lost, Without Recurrence
Cancer of lip	21	5	2
Cancer of tongue	18	2	0
Cancer of floor of mouth	5	3	0
Cancer of buccal mucosa	6	3	1
Cancer of tonsil	4	1	1
Cancer of salivary gland	2	1	1
Cancer of cervical lymph nodes (primary undetermined)	1	0	0
Cancer of skin of head and neck (including melanoma of skin and orbit)	8	0	0
Cancer of lung	1	0	0
Cancer of extrinsic larynx	1	0	0
Lymphosarcoma of neck	1	1	0
Hodgkin's granuloma	2	1	0
	70	17	5

Total number of cases	70	
Lost without recurrence	5	
Total determinate group		65
Five-year survivals		17
Net cure rate (17/65)		26%

Using only proven nodes, end-results could be calculated in more than one way. The efficacy of neck dissection in selected, early, operable cases, all histologically positive (Table VI) is proved by the fact that 26 per cent have survived for over five years. Since all cervical nodes not treated by surgery, including the inoperable and hopelessly advanced and palliative cases, receive radiation, no cure rate percentage can be calculated for any significant comparison with neck dissection. It has been stated, however, by some authors that there is no authentic case of a five-year cure of proven cervical metastases treated by radiation alone. In answer to such statements, I wish to place on record the data given in Table VII. At the Memorial Hospital, 46 patients with histologically proven metastatic cancer treated by radiation alone survived for five years or more. These cases do not necessarily represent all the cures, but only those in which aspiration biopsies were made. To-day aspiration biopsy is part of the routine in all cases; it will be noted that the numbers of proven successes have increased in the later years.

TABLE VII

HISTOLOGICALLY PROVED CASES OF CERVICAL METASTATIC CANCER TREATED BY RADIATION ALONE

Free of Disease March 1, 1939

Five Years or More		Less than Five Years	
Prior to 1930	4	1935	12
1930	5	1936	13
1931	5	1937	19
1932	12		
1933	10		
1934	10		
Total	46	Total	44

DISCUSSION.—DR. WILLIAM F. MACFEE (New York): Doctor Martin's approach to the study of cervical node metastases is somewhat different from that to which some of us are accustomed. Ordinarily, one thinks of the various primary lesions as producing certain percentages of metastases, whereas Doctor Martin presents the percentages of cervical metastases which have been produced by the various primary lesions. Cancer of the floor of the mouth, for example, presents an incidence of cervical metastasis amounting to something like 30 or 40 per cent, if the cases are taken in series as they enter the hospital. As seen from the reverse point of view, 9 per cent of cervical node metastases are produced by cancer of the floor of the mouth.

When one attempts to determine clinically whether the cervical nodes are involved in a particular case he is confronted with a considerable chance of inaccuracy. When the nodes erroneously considered involved are added to those erroneously thought not to be involved, the total error is about 40 per cent.

The simplest solution of the problem of node invasion is either to consider all nodes involved and treat them accordingly, or to regard them as uninvolved until proven to be involved. The first point of view will, undoubtedly, lead to many unnecessary node dissections, as Doctor Martin has indicated, but the opposite point of view will, just as certainly, lead to delay in the treatment of many cases with involved nodes. It may be reasonably questioned whether the uncompromising adoption of either attitude is to the best interests of the patient.

One of the difficulties in statistical presentations on the subject of cancer is the notable lack of uniformity in the selection of cases; one series is often not truly comparable to another. A real advance will be made when statistics on cancer of any part of the body, the tongue or breast, for example, are based upon all the cases observed in a particular clinic over a definite period of time. Subgroupings could then be considered in relation to the whole experience.

It is very encouraging to see that so many patients with cervical node metastases treated by radiation alone have survived the five-year period. Many physicians have acquired the belief that cancer in lymph nodes cannot be destroyed by radiation and it is gratifying to be shown that such is not the case. It cannot be doubted that radiation has a definite usefulness in the treatment of cervical node metastasis, particularly in the group of undifferentiated tumors which occur so frequently in the region of the tonsil and pharynx.

DR. JOHN M. HANFORD (New York): Doctor Hanford said that ten years ago a Head and Neck Neoplasm Clinic had been started at the Vanderbilt Clinic and the Presbyterian Hospital with Dr. A. P. Stout, the pathologist, Dr. Maurice Lenz, the radiotherapeutist, and himself, as surgeon. During

those ten years, Doctor Hanford said, he had become very much impressed with the value of radiation therapy.

To-night certain things were brought out. Doctor Martin did not mention external irradiation by radium; but roentgenotherapy alone apparently cannot be counted upon to cure squamous cell metastatic carcinoma in the cervical lymph nodes. Interstitial treatment by radon, however, has been demonstrated to bring about five-year cures in certain cases. These are real contributions.

There is a great difference between the anterior part of the tongue and the posterior part, as there is, also, between the lip and the tongue. In carcinoma of the posterior part of the tongue, radical neck dissection is rarely indicated. Carcinoma of the anterior two-thirds of the tongue is much more likely to need radical neck dissection, even though no nodes are palpable. Carcinoma of the lip rarely needs treatment of the neck.

Another phase of this subject mentioned by Doctor Hanford was the fact that occult metastases may be present when no nodes are palpable, or when nodes are slightly palpable. One must assume, for example, that in carcinoma of the tongue, there is a high percentage of cervical metastases. Should one await the appearance of a node sufficiently large to be identified as feasible to treat with interstitial radon? This delay and this treatment of only such palpable disease court disaster for the patient. This sort of treatment is a makeshift, and while valuable in certain patients, such as those unsuited to withstand a radical neck dissection, it is not the ideal or the standard method of protecting the patient who has carcinoma of the anterior part of the tongue. The ideal is radical neck dissection, preferably before and certainly after nodes become suspected. The very presence of a node sufficiently large to treat with radon presupposes, even more, the presence of occult metastases. Therefore, the treatment by radon, interstitially, of this palpable metastatic disease must be admitted as incomplete.

The same principles hold in carcinoma of the lower lip, but because cervical metastases from the lip are less common than from the tongue, the indications for treating the neck in lip carcinoma are less compelling.

Doctor Hanford also referred to nodes which are large, firm, extensive or adherent, and recalled that three years ago he presented before the N. Y. Surgical Society a series of patients representing an advanced stage of cervical metastases treated by radical neck dissection. There were more than 7 per cent five-year cures in a few such patients, which means that this "stage three" of Lacassagne is not necessarily hopeless. These patients were treated mainly by surgery. Some had roentgen or radium therapy; but without the surgery any good radiotherapeutist would have admitted they could not have been cured. Surgery, therefore, may play a part in very extensive disease. Even though adherent to the muscle or vein, it is still possible that radical surgery may cure the patient.

Finally, Doctor Hanford felt that the average surgeon using rectal ether anesthesia, in a long neck dissection, with careful hemostasis, gentle manipulation, and with true cancer surgery, is going to do better work than with local or regional anesthesia.

Dr. Hayes Martin, in closing, said that both Doctor MacFee and Doctor Hanford have called attention to the fact that it is sometimes difficult to diagnose metastatic nodes by palpation. Doctor Martin admitted this difficulty, but said he believed that the surgeon's accuracy of clinical diagnosis will steadily improve if he makes a definite preoperative diagnosis in each case, records this diagnosis in writing on the chart, and checks it with the postoperative histologic examination. Aspiration biopsy is useful in doubtful cases, especially where neck dissection would be attended by considerable risk

because of the patient's general condition. In any case, the surgeon should hold himself responsible for the accuracy of his preoperative clinical diagnosis and should consider it a reproach to find too many of his neck dissections negative on histologic examination.

In the diagnosis of metastatic cervical cancer, it is not particularly illuminating to state that the lymph nodes are "not palpable" in a given case. He stated that in his experience, normal lymph nodes are palpable in practically all healthy subjects. The problem is to decide whether or not the palpable nodes have been invaded by cancer.

The question as to whether prophylactic neck dissection is justifiable in the treatment of cancer should, and he said that it seemed to him to be settled only after an analysis of the clinical behavior of large series treated, on the one hand, and by prophylactic neck dissection and, on the other, by a "watchful waiting" policy. Prophylactic neck dissection could benefit only those patients who are admitted without nodes and later develop them. According to such analyses prophylactic neck dissection can be of value in only one case in eight (12 per cent) in cancer of the tongue, and in only one case in 33 (3 per cent) in cancer of the lip. It seemed to him that this percentage was too small to justify routine dissection, especially when the procedure is accompanied by a definite mortality. Under the higher mortality rates for neck dissection (10 per cent), this procedure would kill as many as it could possibly cure—and in some cases more. In any event, it is too serious and costly an operation to be undertaken when the percentage of patients benefited is so small.

Doctor Martin stated that since, from a consideration of his own and other published figures it is obvious that general anesthesia almost quadruples the operative mortality in neck dissection, he failed to see how Doctor Hanford could reasonably maintain his advocacy of rectal ether for this procedure.

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PSEUDOGASTRITIS OF OPERATIVE ORIGIN

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PEPTIC ULCER is believed by many clinicians always to be associated with gastritis, and the latter has been thought to be an important etiologic factor in the production, maintenance, and recurrence of peptic ulcerations. One of the chief arguments in favor of this concept comes from the study of resected surgical specimens.

Recently, Schindler,[1] and his coworkers, have suggested that some of the pathologic changes which have been observed following resection of the stomach were artefacts produced during the gastrectomy. In a series of experiments upon normal dogs these workers were able to reproduce typical gastric changes in devascularized segments of the stomach which contained free hydrochloric acid. They believed that the changes which they observed were produced by the action of the hydrochloric acid on gastric mucosa which had become devitalized during operation. Some years previously, Afendulis and Gulzow[2] reported that following portal venous obstruction in dogs the gastric changes commonly associated with gastritis were observed. They postulated that the gastritis was caused by a circulating toxin, liberated from the damaged liver itself, or from the markedly congested gastro-intestinal tract.

Clinics in this country and abroad have reported[3, 4, 5] a wide variation in the incidence of gastritis in surgical specimens. This can hardly be explained by variations in the concentration of free hydrochloric acid in the stomach. However, individualities in surgical technic permit wide fluctuations in the degree of engorgement encountered in the stomach during the performance of a partial gastrectomy. It seemed important to study whether or not this factor might not be the significant variable accounting for the varying degrees of gastritis observed in surgical specimens.

Methods.—Healthy dogs, weighing between 5.4 and 17.6 Kg., were selected for the experiments. They were fasted for 24 hours before beginning the experiment. Gastric lavage was routinely performed in the first few experiments but so little material was recovered that it was discontinued thereafter. The animals were anesthetized with sodium amytal administered intraperitoneally.

As is well known, the stomachs of fasting dogs commonly contain no free hydrochloric acid. In the experiments in which it was desired to assure the presence of this acid, it was often induced by the administration of one milligram each of histamine hydrochloride and acetyl-beta-methylcholine chloride given

one-half, one, and one and one-half hours before beginning the operation. In other instances 0.1 n. hydrochloric acid in amounts varying from 40 to 80 cc. was injected directly into the stomach cavity by syringe and needle after celiotomy. No difference in the end-results could be distinguished in the results from these two modes of producing an adequate supply of free hydrochloric acid.

In order to eliminate other factors as responsible for the production of gastritis in these studies a series of control experiments was undertaken.

In one dog, following a midline abdominal incision, the stomach was excised *in toto*, rapidly, without the use of intestinal clamps, and without ligating or applying hemostats to the vessels. No free hydrochloric acid was induced, and a negative reaction to Töpfers reagent was obtained from the gastric secretions. The resected segment was placed in a specimen pan for two hours. Biopsies were then taken from various portions of the stomach. These provided sections which we used for later comparison.

Control Experiments.—(1) This group consisted of two animals. The presence of free hydrochloric acid was induced as discussed above. The abdomen was opened by a midline abdominal incision and a soft rubber-covered clamp was loosely applied to the duodenum to prevent the copious acid-containing secretions from passing down the intestinal tract. At the end of two hours, the stomach was excised *in toto*, biopsies were taken from various areas, and the specimens preserved. No significant gross or microscopic changes were found.

(2) This group consisted of five animals. No free acid was induced and none was found present. After a midline incision through the abdominal wall, the pylorus was delivered into the wound and the duodenum was severed between intestinal clamps. An intestinal clamp was applied across the midportion of the stomach; in two instances a rubber-covered clamp, and in three instances a crushing clamp of the Payr type was used. The distal half of the stomach was freed of its vascular attachments. This was done rapidly in order to prevent any unligated artery from continuing to pump blood into the isolated segment and thus produce engorgement. The intestinal clamps were applied for two hours, after which time the stomach was excised *in toto*. Biopsies were taken from various areas of the resected segment. No important gross or microscopic changes were found.

(3) This group consisted of six animals. No free hydrochloric acid was present. It was similar to Group 2, except that in these dogs engorgement of the segment was encouraged. This was accomplished by slowly ligating the vessels and allowing the left gastric artery to pump blood into the otherwise isolated segment for approximately ten minutes before this artery was also ligated. The specimens were left *in situ* and at the end of two hours the entire stomach was excised. Biopsies were then taken. The changes observed were proportional to the degree of engorgement which had taken place (Fig. 1). In the main these consisted of cyanosis and edema of the mucosa. In one instance, in which the left gastric artery was allowed to

pump blood into the otherwise completely devascularized stomach, severe hemorrhages were observed in all coats of the gastric wall. There was massive edema and cyanosis, but the surface epithelium was everywhere intact (Fig. 2).

Experimental Procedures.—Following the completion of the control series, two groups of experiments were undertaken. In both groups the presence of free hydrochloric acid in the stomach was assured by the methods previously described. An attempt was made in both groups to duplicate the

FIG. 1.—Vascular congestion—no hydrochloric acid. Duration two hours. (×230). Note the intact mucosal epithelium and the engorgement of the mucosal capillaries.

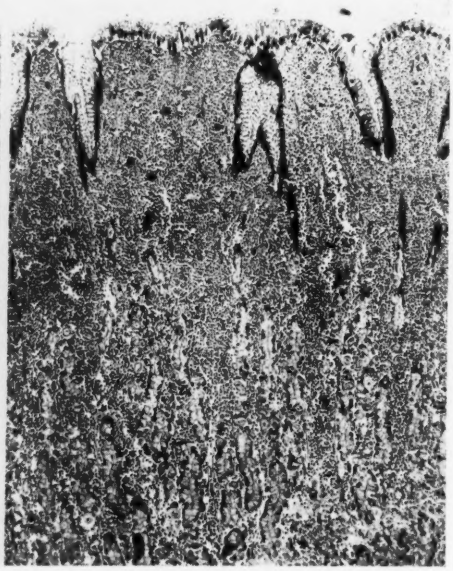

FIG. 2.—Massive congestion—no hydrochloric acid. Duration three hours. (×150). There is extensive mucosal hemorrhage, with compression and disruption of the glandular crypts. The surface epithelium shows no erosion of necrosis.

conditions encountered in the performance of a partial gastrectomy in a surgical clinic.

(A) This group consisted of 23 animals. After a midline abdominal incision, the duodenum was severed between intestinal clamps. The circulation to the distal half of the stomach was rapidly occluded by the simultaneous closure of clamps previously placed across the midportion of the stomach and on the vascular attachments of its greater and lesser curvatures. This technic was designed to prevent vascular engorgement of the distal portion of the stomach. In most instances the resection was not completed but the abdomen was closed over the clamps. At the end of periods varying from 60 to 180 minutes, the incisions were reopened, and, as a rule, the stomach excised *in toto*. In a few instances the completely devascularized segment was immediately resected and then placed in a specimen dish with the clamps and ligatures *in situ*. These specimens were examined after similar periods of time had elapsed and biopsies were taken.

(B) This group consisted of 18 animals and was in all respects similar to the preceding group, except that an attempt was made to encourage engorgement in the portion of the stomach proposed for resection. This was accomplished by placing an intestinal clamp across the midportion of the stomach in such manner as not to occlude the left gastric artery. The duodenum was severed between intestinal clamps. With the exception of the left gastric artery the vascular connections along the greater and lesser curvature of the portion of the stomach proposed for resection were then ligated and divided. The left gastric artery was isolated and was allowed to pump blood for ten minutes into the segment of stomach having no vascular outflow. The stomach was either left *in situ* or, in a few instances, immediately excised with the clamps remaining in place on the resected segment. The specimens were examined in from 30 to 180 minutes after beginning the resection.

In two animals in this group the stomach was filled with 0.1 n. hydrochloric acid and rubber-covered clamps placed across the midgastric area. The arterial ligations were done so that in one dog marked engorgement was produced in the upper half of the stomach while in the other dog only the lower half was allowed to become engorged. The specimens were both examined at the end of two hours.

Biopsies were then taken and the specimens preserved.

TABLE I

RESULTS OF EXPERIMENTS IN WHICH VASCULAR ENGORGEMENT OF THE DISTAL PORTION OF THE STOMACH WAS AVOIDED DURING THE PERFORMANCE OF A PARTIAL GASTRECTOMY

Dog No.	Engorgement		Free HCl	Time in Minutes	Gastritis	
	Gross	Micro.			Gross	Micro.
20	0	0	+	60	0	0
103	0	+	+	65	0	0
101	0	+	+	75	0	0
102	0	+	+	90	0	0
104	0	+	+	90	0	+
17	0	0	+	120	0	+
18	0	0	+	120	0	0
562	+		+	120	+	
108	0	0	+	120	0	+
109	0	0	+	120	0	+
205	+		+	120	+	
202	+	+	+	120	+	++
304	±		+	120	+	
208	0		+	120	0	
201	+	0	+	132	0	0
106	0	0	+	135	0	+
105	0	+	+	142	0	+
408	+	+	+	180	0	0
303	0		+	180	0	
301	0		+	210	0	

Results.—In Table I are charted the results obtained in those experiments in which vascular engorgement was avoided as far as possible. There is a notable absence of gastritis regardless of the time factor and of the presence of free hydrochloric acid (Fig. 3). Minor degrees of gastritis when present were usually associated with slight engorgement which resulted despite our

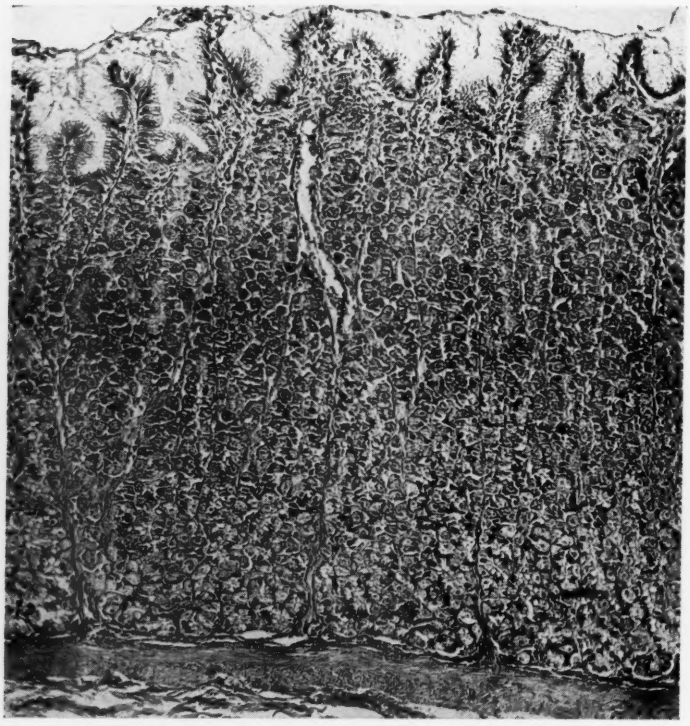

FIG. 3.—No congestion—free hydrochloric acid present. Duration two hours. (×150). The mucosal epithelium is everywhere intact.

TABLE II

RESULTS OF EXPERIMENTS IN WHICH VASCULAR ENGORGEMENT OF THE DISTAL PORTION OF THE STOMACH WAS ENCOURAGED DURING THE PERFORMANCE OF A PARTIAL GASTRECTOMY

Dog No.	Engorgement		Free HCl	Time in Minutes	Gastritis	
	Gross	Micro.			Gross	Micro.
19	++	+++	+	30	+	0
21	++	++	+	30	+	+
22	++	++	+	45	+	0
14	+++	+++	+	60	+++	+++
5	++	+	+	75	+	+
6	++	+++	+	120	+	++
12	+	+	+	120	+	+
107	++	+++	+	120	+++	+++
206	+	++	+	120	++	0
13	++++	++++	+	120	++++	++++
8	+++	+++	+	120	++++	+++
15	+++	++++	+	120	++++	++++
16	++++	++++	+	120	++++	++++
204	+	+	+	125	+	+
209	++	++++	+	125	++	+++
310	++	++	+	150	+	++
305	++++	++++	+	150	++++	++++
307	+++	+++	+	150	+++	+++
409	+++	++	+	180	++	+
308	++	++++	+	180	++	+++
309	++	++++	+	180	+++	+++

attempts to prevent it. In the majority of these specimens a tenacious white film of exudate covered the mucosal surface but no other changes were noted. This film was found to consist of coagulated mucin (Fig. 4).

FIG. 4.—No congestion—free hydrochloric acid present. Duration two hours. (×150). Note the absence of vascular congestion and the amorphous exudate on the surface of the undamaged epithelium.

In Table II are given the results obtained in those experiments in which vascular engorgement was encouraged in the presence of free hydrochloric acid. The high incidence of gastritis in this group was proportional to the degree of engorgement. Gastritis was slight or absent in those experiments in which the time interval from beginning the resection to examination of the specimen was less than 60 minutes. In the process of devascularization of the entire stomach of two animals in this group, marked engorgement was produced in the upper half of the stomach in one, while in the other, only the lower half was allowed to become engorged. At the end of two hours only the engorged segments showed evidences of gastritis.

Gross Pathology.—The typical gross pathologic features of the gastritis

observed in these experiments consisted of varying degrees of mucosal edema and cyanosis, petechial and major hemorrhages on the mucosal surface, and superficial erosions. In all cases an exudate covered the mucosal surface. This exudate, composed of coagulated mucin and cellular débris (Fig. 5), and stained with acid hematin varied in appearance and consistency, but was usually mottled greenish- or brownish-white in color. The fluid contents of the isolated segments were streaked with a small collection of brownish acid hematin.

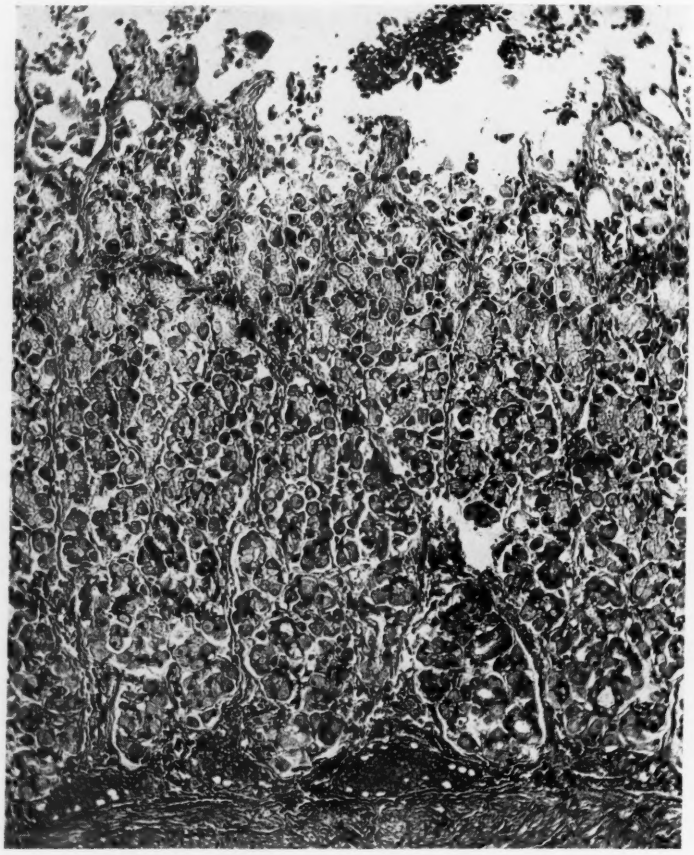

FIG. 5.—Vascular congestion—plus hydrochloric acid. Duration one hour. (×150). There is erosion of the mucosa. The exudate is composed of cellular débris and erythrocytes.

Histopathology.—The characteristic microscopic findings consisted of varying degrees of erosion, mucosal and submucosal engorgement, and edema. We did not observe the leukocytic infiltration of the mucous membrane described by Schindler,[1] and others.[5, 6] In many instances eroded mucosal capillaries could be seen, in the lumina of which hemoglobin had been changed to acid hematin by the action of hydrochloric acid (Fig. 6).

Discussion.—The destructive action of the hydrochloric acid of gastric juice upon devitalized tissue has long been recognized. The work of Mor-

ton,[7] and Dragstedt[8] has demonstrated the importance of the blood supply in preventing digestion of portions of liver, spleen, and kidney transplanted into the gastric wall. Schindler's experiments suggest that anemia is the devitalizing factor responsible for the striking changes produced by the action of hydrochloric acid on the devascularized gastric segment.

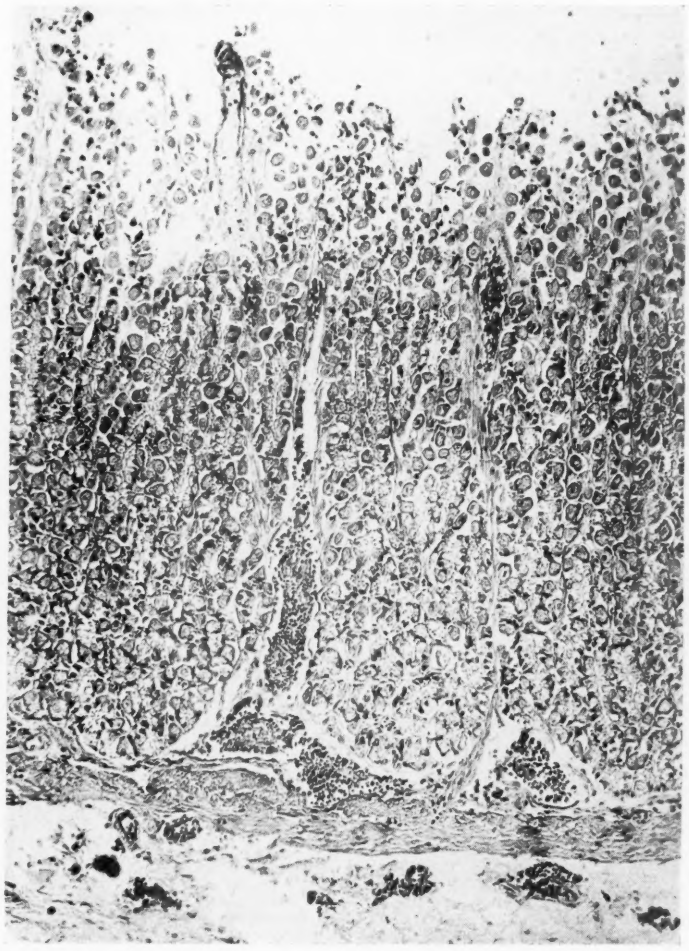

FIG. 6.—Vascular congestion—plus hydrochloric acid. Duration two hours. (×150). There is marked erosion and superficial destruction of the mucosal epithelium. Three mucosal capillaries are shown to have been tapped by the erosive process. The stained section demonstrates that the hemoglobin of the erythrocytes contained in these vessels has been changed to acid hematin.

Afendulis and Gulzow[2] were able to produce similar changes in living animals following experimental stenosis of the portal vein. Their animals survived for periods of from four to six weeks, and well-defined gastritis was present as early as five to eight days postoperatively. Changes were most marked in the fundus and corpus, while the antrum was relatively unaffected. The animals were periodically gastroscoped throughout their postoperative course and, in several instances, subsidence of gastritis was

found at autopsy to coincide with the development of an efficient collateral circulation. Severe chronic passive congestion of the abdominal viscera was present in all animals showing gastritis. Foci of necrosis were seen in the liver in many animals. Afendulis and Gulzow suggested that toxic split-products of protein which attacked viscera already devitalized by the asphyxia of congestion, were liberated either from the damaged liver or from the chronically congested gastro-intestinal tract. They supported this contention by supposedly demonstrating an abnormally high histamine level not only in the portal but in the systemic venous blood of their animals. Periodic gastric analyses showed hypersecretion of acid. Konjetzny[9] also endorsed the theory that engorgement predisposed to gastritis by lowering the vitality of the gastric mucosa. He too recognized the necessity for a second, toxic factor, but was unable to specify its nature.

Our findings and those of Schindler and his associates strongly suggest that the toxic agent postulated by Konjetzny, and by Afendulis and Gulzow, is hydrochloric acid and that asphyxia is the devitalizing factor which renders the gastric mucosa vulnerable to the action of this agent. The present experiments demonstrate that while erosion of the mucous membrane may occur in the presence of hydrochloric acid, in the nonengorged devascularized stomach it proceeds much more rapidly when vascular engorgement is present. Under such circumstances there are also present the additional phenomena of the profuse exudation and hemorrhage. Erosion of an engorged mucosa can be expected to produce greater hemorrhagic manifestations than a similar process in a nonengorged mucous membrane. A clearer conception of these phenomena may result if one considers the engorged, devascularized segment as a large, blood-soaked sponge, which, by erosion of its surface membrane, decompresses itself by bleeding from the open pores of its mucosal capillaries. This concept is supported in our experiments by the constant finding of acid hematin in the contents of those stomachs showing engorgement and gastritis, while the contents of those stomachs in which gastritis and engorgement were minimal contained only clear fluid.

The predilection of gastritis in these experiments for the mucosa of the corpus, corroborates the findings of Afendulis and Gulzow. The reason may be that the mucosa of the antrum and *magenstrasse* in the dog is more firmly bound to the underlying muscularis and is more compact, permitting less engorgement of these areas. This selective distribution of edema and engorgement was evident in those control experiments in which the effect of engorgement alone was studied. In addition, the predominance of mucous cells in antral epithelium may afford a measure of protection against erosion in this area. These regional differences in structure are not so definite in the human, which may at least in part account for the "antral gastritis" described in specimens of the resected human stomach.

Time was demonstrated to be an important factor in these experiments. Reference to Table II shows that a minimum time-interval of 60 minutes between the commencement of devascularization and the examination of the

FIG. 7.—Dog's stomach excised *in toto*. Free hydrochloric acid introduced into both the distal and proximal compartments. Congestion only in distal compartment. Note distribution of engorgement and gastritis in distal segment, tending to avoid antrum and *magenstrasse*.

specimen was necessary for the appearance of gastritic changes in the engorged stomach, and that the maximum changes were reached in between 60 and 120 minutes.

How far does the operation of subtotal gastrectomy, as performed in various clinics reproduce conditions of devascularization, engorgement, and time, which we found necessary for the production of gastritic change? The answer to this question resolves itself into an appraisal of the various features of the operative procedure which might contribute to the production of engorgement of the segment to be resected.

The procedure of delivering the stomach from the abdominal cavity to facilitate resection, may at the same time increase gastric engorgement by hindering venous return. The placing of large gauze packs may likewise obstruct venous return by compression of the regional veins.

By far the greatest cause of congestion, however, is most frequently found in the actual procedure of resection itself. The usual technic calls for careful ligation of all the blood vessels to the portion of the stomach to be resected, beginning at or near the pylorus, and proceeding toward the cardia. The left gastric vessels are usually the last to be ligated, after which a crushing or rubber-covered clamp is usually placed across the stomach at the level of the proposed resection. The procedure has the effect of progressively converting the distal portion of the stomach into a closed vascular sac, into which the left gastric artery has been allowed to pump blood for from 10 to 45 minutes, depending upon the speed of the surgeon and the actual technic employed.

The time elapsing between the beginning of resection and the examination of the resected specimen is important. The actual time of resection may be short but the specimen may be relegated to a specimen basin for some time before examination. On the other hand the resection time may be prolonged, but the resected specimen may be examined promptly on removal. In both instances, the total time-interval may exceed the critical period for the appearance of gastritis, which we have shown in dogs to be 60 minutes. It is interesting to note that removal of the clamps from the cut surfaces of the resected specimen, or opening the specimen before a certain time has elapsed, allows vascular decompression of the viscus, and reduces the incidence of gastritis. One might expect, therefore, slightly greater congestion, and consequently more marked gastritis, if crushing clamps are used during the resection.

SUMMARY

The incidence of gastritis reported from different clinics and from different countries varies widely. Schindler, and his coworkers, suggested that the gastritis observed was an artefact produced by the technic of gastric resection in the presence of free hydrochloric acid.

In the present work it was demonstrated that when free acid was present in the stomach of the dog, gastric changes were (1) proportional to the

degree of gastric vascular engorgement which occurred during operation; and (2) to the time elapsed between beginning the resection and the examination of the specimen. The technic of gastrectomy as employed in surgical clinics can reproduce these conditions.

The present work seems to indicate that gastroscopy rather than the study of surgically resected specimens should be the basis for the evaluation of the frequency of the coexistence of peptic ulcer and gastritis.

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RUPTURE OF THE STOMACH FOLLOWING INGESTION OF SODIUM BICARBONATE

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SPONTANEOUS SUBCUTANEOUS RUPTURE of the stomach, unassociated with trauma of the abdominal wall or with preexisting pathologic lesions of the stomach itself, is an unusual and interesting condition. We frequently encounter rupture of the stomach as a result of perforating ulcers, and such injuries as gunshot or stab wounds or other direct localized trauma to the abdominal wall, and, for this group, understand the mechanism involved. We herewith present a case of spontaneous rupture of the stomach; review the literature on the subject; and discuss the possible mechanism of such a catastrophe.

Rupture of the stomach as a result of trauma to the abdominal wall, without a penetrating wound, is seen not infrequently; and N. J. Wolf[1] has reviewed 46 such cases. Rupture of a solid viscus (liver, spleen, pancreas, kidney) or of the small bowel, is not uncommon following severe crushing violence to the abdomen, but the stomach almost invariably escapes injury. It seems logical that the elastic, loosely-attached pliable walls of the stomach readily and rapidly accommodate the organ to the abrupt change in intra-abdominal pressure and configuration, and the gas bubble at the cardia does not exert sufficient counterpressure to cause a bursting rupture. The cardiac and pyloric orifices, too, permit an escape of the stomach contents and allow for a rapid decompression. Ritter[2] has done experimental work to support this contention by delivering repeated, forceful blows on the upper abdomen of dogs without producing a gastric rupture. Vanni[3] showed that trauma over the overfilled stomachs of dogs produced only mucosal tears. In some cases, it is true, the human stomach may be torn at its attachments, but usually the sudden displacement and change of pressure is not sufficient to tear this flaccid and mobile organ. In most cases of traumatic rupture of the stomach, without abdominal wall penetration, the stomach was distended with food and gas. Filling, or overfilling, of the stomach produces a more or less fixed shape, reduces mobility, and predisposes to rupture. Trauma at such a time, if there is sufficient distention and if the wall itself has undergone certain reversible changes which approach a pathologic state, will cause a tear in the wall of the stomach, usually at or near the lesser curvature. Cardiospasm or pylorospasm must be considered as contributory factors since this would tend to deprive the stomach of their safety valve effect. Glassman[4] points out that if the contents of the stomach can escape through the cardia or pylorus

the fatal increase in pressure at the moment of trauma can be avoided. "The tonicity of these openings is controlled by a nervous mechanism which is not easily and suddenly overcome and may be increased by pylorospasm or cardiospasm."

The mechanism of rupture without trauma, on the other hand, is somewhat more complex, and one is inclined to suspect mild trauma or an unrecognized pathologic lesion of the wall, especially ulcer. Most of the cases reported in the nineteenth century literature were probably not ruptures of the normal stomach, and Cruvillier's[5] exposition of the condition, now easily diagnosed as perforated peptic ulcer (1832), did not clear the literature of these unreliable case reports until the latter part of the century. The progress of surgery, with opening of the abdomen, and more frequent postmortem examinations are responsible for an increase in our knowledge pertaining to this uncommon condition. It is also true that mild force can, under special circumstances, cause disruption of the stomach, and that mild trauma may be forgotten by the patient who is suffering severe peritoneal pain. Conversely, mild trauma may be coincidental or suggested to the patient.

The normal collapsed stomach, in a state of physiologic rest, is not subject to rupture. A traumatic rupture occurs as a result of overdistention. With progressive overfilling of the stomach, there first occurs a tonic physiologic relaxation. When the limits of this state have been reached, further additions to the gastric content cause overfilling, with an atonic stretched and thinned wall, and perhaps mechanical mucosal tears. Busch,[6] on the other hand, believes rupture occurs more frequently with tonic rather than atonic dilations. With overdistention there is interference with the circulation of the gastric wall, and areas of softening occur. Talma,[7] in rabbit experiments, showed that with overdistention areas of softening and infarcts are produced, and a small amount of HCl will cause ulcers and necrosis in such stomachs. These changes are probably reversible. Rupture occurs as a result of the mounting pressure from within exerted on the weakened and thinned wall. The final increment of pressure may be of a sudden nature and is probably gaseous due to rapid release of fermentation gases or from carbon dioxide after ingestion of sodium bicarbonate. Murdfield[8] has shown that the sudden increase of gas pressure produced by adding some sodium bicarbonate to two or three liters of weak HCl will regularly produce ruptures of cadaver stomachs, or at least submucosal tears. (This observation is of particular interest since the case we report was precipitated by, or followed the ingestion of sodium bicarbonate.) The final increment of pressure may be from without the stomach, as in the case of traumatic ruptures, further emphasizing the pathophysiologic similarity of the two conditions. Miller[9] reports a case of spontaneous rupture of the stomach during labor, in which the pressures of vomiting, straining, and a supporting Beck corset resulted in a three-centimeter ragged perforation at the midportion of the greater curvature. Vomiting was an "onset" symptom in several of the abstracted cases. Hutyra and Marek[10] believe that rupture of the stomach may occur in horses from the

violent contracture of the gastric musculature. Weiss and Mallory[11] report ten cases of laceration near the gastric cardia following alcoholism and vomiting, and believe that pressure changes in the stomach are responsible.

In spontaneous ruptures pylorospasm and cardiospasm are probably present, which prevent the escape of the distending contents. It is apparent that some factor must interfere with the normal emptying of the stomach, or emptying by emesis, or overdistention beyond the limits of elasticity cannot occur. In this connection, it is interesting to note that many cases of gastric rupture have been reported, in which a pathologic lesion of the esophagus, pylorus, or duodenum served to block the pressure-releasing mechanisms and a spontaneous rupture occurred in a nondiseased area, apparently by the above described mechanism. Among this type is a case reported by Cavaillon and Leriche[12] of a stenosing carcinoma of the pylorus. After a heavy meal, a gastric lavage was attempted, resulting in a perforation in an undiseased area of the anterior wall near the lesser curvature. Cannon and Halbert[13] report the occlusion of a previously patent valvular stenosis of the duodenum, with acute dilation and rupture of the normal stomach. A tear 1.5 cm. was produced about 2 cm. from the cardiac orifice. Seegar and Shulz[14] report a case of spontaneous rupture in an infant of 17 months. At autopsy, an obstructing band was found 20 inches below the pylorus. Wunschheim[15] reports a case in a patient whose stenosing esophageal neoplasm prevented vomiting. There was a tear two inches long from the cardia parallel to the lesser curvature. Rupture of the stomach when incarcerated in a diaphragmatic hernia has been reported by Berard and Gallois,[16] and indicates that some damage or obstruction to the stomach's openings may have followed from its abnormal position. These cases illustrate the fact that an obstruction to one or the other of the stomach's orifices is an important factor in the production of a gastric rupture.

Oscar Glassman[4] reports 14 cases of spontaneous rupture of the stomach. Of these, two were operated upon, and one recovered. The others died. Wolf's[1] review, in 1936, lists 17 cases, some of which are from Glassman's series. We have found 13 additional cases which can definitely be considered spontaneous ruptures of the stomach. This makes a total of 30 cases to which we add the one herewith reported. Of these 31 cases only five were operated upon. There were two recoveries. Since 1911, there has been no such case admitted to the Jefferson Hospital in Philadelphia. However, there have been two cases of spontaneous rupture of lower end of the esophagus, near the cardia, which revealed no existing pathologic lesion at postmortem. One similar case was found among the records of the Philadelphia General Hospital, covering the records for the past five years.

Pathology.—The rupture of the gastric wall usually occurs on the lesser curvature. A number of the cases reported do not specifically locate the site of the tear. As Key-Aberg[17] points out, with distention the stomach tends to assume a spherical shape. Therefore, the lesser curvature is stretched most

and tears first. Cavaillon and Leriche[12] advance a similar explanation and demonstrate this localization of tears on dogs. Frankel[18] believes the absence of mucosal folds on the lesser curvature plays a rôle. A second common site is the anterior wall near the fundus. The tears present clean edges, vary in length, and may extend into the esophagus. At operation or postmortem the stomach is usually found to be greatly distended and there is gross contamination of the peritoneal cavity with undigested and partially digested food and liquids. Microscopic study of the gastric wall shows thinning, capillary hemorrhages, and early muscular degeneration.

Clinical Picture.—The patient presents the picture of an overwhelming abdominal catastrophe. There is often a history of dietary or alcoholic debauchery. The patient may or may not describe a sudden onset of pain. In some cases a sensation of "giving way" or a "bursting noise" has been heard.[19] Shock and prostration predominate, the abdomen has a peculiar rigidity and diffuse tenderness, and peristalsis is absent. Subcutaneous emphysema was noted in a number of the cases. This was true of each of the three cases of spontaneous rupture of the lower end of the esophagus mentioned, and accompanied those cases of spontaneous rupture of the stomach in which the tears extended into the esophagus, and which were due to migration of gastric gases into the mediastinum.

Diagnosis.—This has not been made preoperatively in any case of spontaneous rupture of the stomach. However, the diagnosis of ruptured esophagus was confirmed at autopsy in one case. Of the 31 cases reviewed, only five were operated upon, and two recovered. Though the course is usually one of rapid death from generalized peritonitis, in two cases there was spontaneous recovery, with abscess and fistula formation.

Case Report.—G. K., white, an obese female, age 51, weighing 220 lbs., was admitted to the Philadelphia General Hospital, July 29, 1939, at 12:05 A.M. She had been overeating and drinking alcoholic beverages since July 21, 1939. On July 26, 1939, she suffered vague upper abdominal pains but was relieved by vomiting. On July 28, before dinner she had "several drinks" and then ate a "very heavy" meal of macaroni, meat balls, cheese, tomatoes, potatoes, bread, pie, water and three glasses of grape juice. A little later she drank some whisky. She began to feel quite bloated and had "heavy feelings" in her abdomen. To relieve this she took "several teaspoonsful of sodium bicarbonate in a glass of water and drank it down." Immediately after this she felt a sudden, severe, generalized abdominal pain which "doubled her up." It continued unabated, with periods in which the pain was referred to the right shoulder. She vomited repeatedly up to the time of her admission, the vomitus containing small quantities of blood mixed with fluids and particles of food.

On examination, she appeared in shock, pulse 140, respirations 32 and were shallow and rapid, temperature 99° F. Blood pressure 138/96. She was doubled up with pain, and her forehead was beaded with a cold perspiration. The right breast was absent (amputated in 1930 for cyst). The heart was essentially negative. The lungs were normal. There was generalized tenderness of the abdomen with corresponding rigidity. The rigidity was somewhat less than the "board-like" character seen in perforated ulcer. Peristalsis was absent throughout, though the patient's uncontrolled grunting made this observation difficult. A large mass which we thought to be a large uterine myoma was present in the lower abdomen.

Leukocyte count was 14,900, 74 per cent polymorphonuclear neutrophils, 22 per cent lymphocytes, 3 per cent mononuclears, and 1 per cent eosinophils. Blood urea nitrogen 17 mg. per cent. A flat film of the abdomen showed that "there apparently is considerable air under both diaphragms. The stomach appears considerably dilated and distended with gas, and there are several loops of colon with gas demonstrable. No evidence of acute obstruction."

In an effort to improve the patient's condition preoperatively, treatment was instituted which consisted of Wangensteen suction-drainage of the stomach and intravenous administration of glucose in normal salt solution. In spite of this, she grew rapidly

FIG. 1.—A diagrammatic drawing to show the distended stomach and the greatly distended lesser peritoneal sac. An overflow is noted through the epiploic foramen.

worse so that her temperature was 104° F. at 2 P.M., at which time her abdomen was opened under continuous spinal anesthesia.[20] It was then approximately 14 hours after her admission, and about 12 hours after air had been demonstrated in the peritoneal cavity. In retrospect, we must condemn the delay in bringing this case to operation, for this case represents an example of inexcusable postponement of operative treatment while waiting for improvement in the general condition to be brought about by use of the Wangensteen tube and other conservative measures. While the patient presented an obscure and confusing diagnostic problem, it is now obvious that her chances of recovery would have been greatly enhanced had operation been undertaken soon after her admission.

On opening the abdomen large quantities of partially digested food were found present throughout the greater and lesser peritoneal sacs. The gastrohepatic omentum was greatly distended (Fig. 1), and seemed to confine most of the gastric contents to the

lesser sac. This may explain the peculiar rigidity noted on the first examination. The gastrohepatic omentum was opened and the free fluid and particles of food were aspirated (3.5 liters) and wiped from the greater and lesser sacs of the peritoneal cavities. A tear, approximately five inches long, was found situated on the lesser curvature (Fig. 2). It involved the lower one and one-half inches of the esophagus and ran downward toward the pylorus. No evidence of any pathologic lesion in the stomach or esophagus could be found. The laceration was closed with considerable difficulty, and the suture line re-

FIG. 2.—A drawing showing the cut gastrohepatic omentum, exposing the lesser sac, and the rupture involving the lower end of the esophagus and extending along the lesser curvature.

enforced with the divided gastrohepatic omentum. A cigarette drain was placed in the lesser peritoneal cavity and two cigarette drains were carried out through a stab wound in the suprapubic area. During the operation, the patient received a transfusion of 400 cc. of citrated blood. She left the operating table with a blood pressure of 110/70, pulse 125, respirations 25. Toxemia and peritonitis progressed rapidly and the patient died six hours after operation, approximately 24 hours after the onset. Permission for autopsy was refused.

SUMMARY

(1) A case of rupture of the stomach following the ingestion of sodium bicarbonate is submitted, with a review of the material found on spontaneous rupture of the stomach.

(2) Rupture of the healthy stomach is an unusual condition. It has not been diagnosed preoperatively or before autopsy.

(3) The factors concerned with the possible mechanism of this catastrophe are discussed.

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PRELIMINARY COLOSTOMY IN THE MANAGEMENT OF GASTROCOLIC AND GASTROJEJUNOCOLIC FISTULAE

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AT A MEETING of the American Surgical Association in May, 1939, Pfeiffer,[8] of Philadelphia, and Kent, of Norwich, reported a method of handling patients suffering with gastrojejunocolic fistulae which throws a new light upon the pathologic physiology of this condition, and suggests the possibility of lowering the high mortality of surgical treatment. They happened upon this procedure almost by accident. One of their patients who had a gastrojejunocolic fistula was given a barium meal which failed to pass from the stomach into the colon. However, barium given by enema passed readily into the jejunum and stomach, demonstrating a ball-valve type of fistula. At operation, the fistula was found to be surrounded by dense adhesions and marked inflammatory reaction. It was decided to perform a preliminary colostomy, on the theory that since the flow through the fistula was in one direction only, namely, from colon to stomach, a colostomy would divert the fecal stream and make subsequent operation upon the fistula easier. After an ascending colostomy was performed the diarrhea ceased entirely, and the patient picked up surprisingly in weight and strength. This was not in accord with the accepted theories regarding the cause of diarrhea in these cases, namely, that it is due to the emptying of acid stomach contents into the colon. Rather, it would appear that regurgitation of colonic contents into the upper gastro-intestinal tract sets up a severe enteritis and consequent diarrhea. A few months later, at operation, the inflammatory reaction around the fistula was found to have subsided almost completely, the tissues were in more nearly normal condition, and the operation for correction of the fistula was carried out more simply than it could have been previously. After simple closure of the gastro-enterostomy, colonic and jejunal fistulae, the patient made an uneventful recovery. The colostomy was closed at a later date. These authors reported one other patient of their own and one of Dr. Ralph Colp's, both with similar courses following preliminary colostomy. Our interest in this subject began in September, 1939.

ILLUSTRATIVE CASES

Case 1.—V. S., white, male, age 59, entered the San Francisco Hospital, May 13, 1936, complaining of continuous vomiting of foul material for two months, diarrhea with as many as 16 bowel movements daily, and loss of 50 pounds in weight. He had had a posterior gastro-enterostomy in May, 1930, for a persistent duodenal ulcer. He was well for two years following the gastro-enterostomy when he suddenly experienced severe epigastric pain lasting about 24 hours associated with abdominal tenderness. Subsequently

there occurred nocturnal diarrhea, and he noted large amounts of undigested food in the stools, followed by extreme weakness and a loss of 50 pounds in weight. A gastro-jejunocolic fistula was demonstrated by barium enema.

Operation.—June 11, 1936: The fistula was found and was repaired by dissecting the colon free from the gastro-enterostomy and closing the fistulous openings in the colon and in the jejunum. The patient was left with the original gastro-enterostomy. After a stormy convalescence he was free from diarrhea but continued to have marginal ulcer symptoms, regardless of diet.

Upon reentry to the San Francisco Hospital in September, 1939, he weighed 97 pounds (his best weight had been 180 pounds). Physical examination revealed a pallid, dehydrated, markedly emaciated adult male with evidence of generalized arteriosclerosis. Peristalsis was hyperactive visually and audibly. There was an old healed upper midline scar extending from the xiphoid to the umbilicus. There was a healed right inguinal scar and a McBurney incision scar which herniated with increased intra-abdominal pressure. Urinalysis, complete blood chemistry, blood Wassermann and Kahn were negative. Examination of the blood at first showed evidence of marked dehydration and later a mild secondary anemia. Barium enema revealed a fistulous communication between the mid-portion of the transverse colon and jejunum which filled the stomach and jejunum with barium simultaneously. Gastroscopic examination did not disclose the fistula. Barium by mouth emptied through the gastro-enterostomy and passed from the jejunum into the colon.

First Operation.—On October 10, 1939, the cecum was brought out of the abdomen, and was opened on October 11. With the opening of the cecostomy the diarrhea immediately stopped. Charcoal given by mouth appeared in the cecostomy after 15 hours. The patient began to gain weight and strength immediately and all vomiting stopped. Barium by mouth, October 30, 1939, 20 days following the cecostomy, revealed the gastrojejunocolic fistula, and so did a barium enema given December 29, 1939, two months later. The patient gained from 97 pounds upon entry to 131 pounds in less than two months. All of the patient's symptoms had disappeared.

Second Operation.—January 16, 1940: Under cyclopropane anesthesia, the upper midline abdominal scar was excised and the abdomen opened. There were many adhesions. The stomach was found to be large and dilated; the duodenum was very narrow, fibrous and contracted, measuring less than 1 cm. in diameter. Palpating through the stomach wall, a stoma could be felt between the stomach and a loop of proximal jejunum and also between the transverse colon and jejunum. The inflammatory changes usually found about this type of lesion were completely absent. A jejunocolic fistula measuring about 3 mm. in diameter was found. The colon was dissected free and closed transversely with chromic sutures. The gastro-enterostomy was taken down and, after resection of three-quarters of the stomach, a Pólya type of posterior anastomosis was made, using the combined opening in the jejunum left by the previous gastro-enterostomy and jejunocolic fistula. The patient made an uneventful recovery. On February 13, 1940, the cecostomy was closed. The patient has since remained well.

Case 2.—W. A., white, male, age 42, entered the San Francisco Hospital, January 2, 1940, complaining of severe pain in the epigastrium relieved by vomiting of fecal material and belching of gas with fecal odor, both of two months' duration. During the past month he had had five to six liquid bowel movements daily, and had lost 17 pounds in weight. He was so weak he could not walk. From the age of 14 he had suffered with stomach trouble, characterized by burning epigastric pain and sour eructations relieved by soda. In 1923, a gastro-enterostomy was performed in the Buffalo City Hospital. He was well for one year after which his symptoms returned. In 1932, 1934, and in 1937 he had suffered with severe gastric hemorrhages, requiring transfusions.

Physical Examination.—The patient was markedly emaciated, and his fingers were slightly clubbed. The breath was very foul. The thorax was poorly nourished, with poor expansion of both sides. There was impaired resonance over both apices. Both bases were hyperresonant. No râles were heard. Blood pressure 120/80. Heart negative. The

abdomen was scaphoid, with an oblique right upper quadrant scar and a transverse right lower quadrant scar. Both upper quadrants were slightly rigid and tender to pressure, especially on the left. Peristalsis was markedly hyperactive. *Laboratory Data:* Blood chemistry negative. Mild secondary anemia. Blood Wassermann and Kahn negative.

Gastroscopic examination revealed an atrophic gastric mucosa. No pyloric activity was seen. The gastro-enterostomy could not be seen. A barium meal, January 8, 1940, revealed a gastrojejunocolic fistula. Methylene blue given by mouth appeared in the stool after one hour and 30 minutes. Gastric analysis disclosed a complete absence of free HCl, and a highest total acid of 20° at ten minutes. On January 13, 1940, the gastro-colic fistula was demonstrated by barium enema.

First Operation.—Under local anesthesia, a loop-colostomy was performed on the right side of the transverse colon, which was opened in bed a few days later. The diarrhea stopped immediately following the opening of the colostomy. In spite of an advanced bilateral pulmonary tuberculosis this patient gained 18 pounds after the colostomy was performed.

Second Operation.—August 1, 1940: Under spinal anesthesia, the abdomen was opened through a left paramedian upper abdominal incision. Although many adhesions were encountered, there was a remarkably small amount of inflammatory reaction about the old gastro-enterostomy. A small fistula was found connecting the anterior margin of the gastro-enterostomy opening and the posterior wall of the colon. The colon was freed and the fistulous opening closed with chromic gut. The gastro-enterostomy was taken down and the opening in the jejunum closed with chromic catgut. A gastric resection was then performed, removing about three-quarters of the stomach.

In spite of the fact that this patient was suffering with an extensive pulmonary tuberculosis, the postoperative course was not remarkable. On the fourth postoperative day he started taking nourishment by mouth, and after the sixth postoperative day he remained afebrile. The abdominal wound healed by first intention.

Because of some difficulty experienced with the colostomy in this patient, we were able to observe the influence of stool in the distal segment of the colon upon the frequency of bowel movements both by rectum and colostomy. Whenever the distal segment of colon was free of stool the diarrhea stopped. This seemed to us to be rather conclusive proof that Pfeiffer was right in his contention that the diarrhea in these patients was not due to gastric contents getting into the colon but rather due to colonic contents regurgitating into the upper gastro-intestinal tract causing hyperperistalsis in the small bowel and consequent diarrhea. The fact that methylene blue taken by mouth appeared in the stool after one hour and 30 minutes would also make one believe that it had passed through the gastro-intestinal tract very rapidly rather than directly from the stomach into the transverse colon.

Case 3.—J. D., white, male, age 39, entered the San Francisco Hospital, January 31, 1940, complaining of diarrhea of two months' duration. In 1929, he had had a sudden severe onset of epigastric pain and was operated upon for a perforated peptic ulcer. A gastro-enterostomy was performed and the ulcer was closed. Since that time the patient suffered with continuous ulcer symptoms. In 1938, he reentered the hospital and a marginal ulcer was demonstrated but he was not operated upon. About two months before his last entry a diarrhea suddenly developed which gradually increased in severity. With the onset of diarrhea all pain disappeared but he began to belch fecal-smelling gas and had occasional attacks of vomiting.

Physical Examination.—The patient was thin and pallid, with a scaphoid abdomen which showed two celiotomy scars. Peristalsis was violently hyperactive. Barium enema

revealed a gastrojejunocolic fistula. Barium meal failed to demonstrate the fistula but showed very rapid filling of the small bowel both through a gastro-enterostomy opening and through the pylorus. The barium was seen to enter the large bowel after 30 minutes.

First Operation.—February 3, 1940: A loop-colostomy was established in the right side of the transverse colon, which was opened in bed four days later. The diarrhea stopped immediately following the opening of the colostomy. Five weeks after the colostomy the patient had gained from 103 pounds to 119½ pounds.

Second Operation.—March 21, 1940: The abdomen was opened through the old midline upper abdominal incision. Many adhesions were encountered but the region of the gastrojejunocolic fistula was remarkably free of inflammatory reaction. A very large fistulous opening was found between the jejunum and colon, apparently beginning at the margin of the gastro-enterostomy. The opening in the large bowel measured about 5 cm. The colon was dissected free and closed transversely with chromic sutures. The gastro-enterostomy was then taken down and, after resection of about three-fourths of the stomach, a posterior Pólya type of anastomosis was made, using the original opening in the jejunum for the anastomosis. An old healed scar of a marginal ulcer was removed from the edge of the opening in the jejunum before the anastomosis was undertaken.

This patient did well following the resection, with the exception that the proximity of the colostomy to the midline wound caused some infection and delayed healing. On April 5, 1940, about two weeks following the gastric resection, a barium enema revealed some narrowing of the transverse colon at the site of the previous fistula. Barium flowed from the superior margin of the distal end of this narrowed segment into what appeared to be a sinus tract leading upward toward the greater curvature of the stomach, but no barium entered the stomach.

Third Operation.—May 23, 1940: The colostomy was closed.

This patient demonstrated three important points: First, that barium given by mouth passes very rapidly through the irritated small bowel; second, that even though some leakage may occur from the site of repair in the colon, preliminary colostomy will prevent disaster from this leakage; and third, that diarrhea will occur in these patients even though a fistula cannot be demonstrated by giving barium by mouth.

In their original article reporting this procedure, Pfeiffer and Kent mentioned that upon reviewing the literature a single instance was found in which colostomy was employed as a preliminary measure to the correction of gastrojejunocolic fistula: *viz.,* Colucci[4] reported a cecostomy performed upon a patient with symptoms suggesting intestinal obstruction. A gastrocolic fistula was later demonstrated, and was apparently the result of spontaneous perforation of a gastric ulcer into the colon. The symptoms of bowel obstruction in this case brought to mind a patient seen at the San Francisco Hospital in October, 1938. He had been transferred to us from another hospital where he had undergone an appendicectomy because of vague gastro-intestinal symptoms, with local findings suggesting appendicitis. The appendix was found to be normal but the cecum was indurated at its base, suggesting a previous rupture, with abscess formation. Following appendicectomy there developed generalized peritonitis and, later, intermittent attacks of bowel obstruction and a left lower quadrant abscess. The abscess was drained. A fecal fistula developed in the appendicectomy wound and in that following drainage of the abscess. At no time did this patient have diarrhea. Three

days after entry to the San Francisco Hospital a gastrocolic fistula was demonstrated, both by barium enema and with barium given by mouth. Tissue removed from the walls of the fecal fistulae showed tuberculous granulation tissue and tubercle bacilli. Roentgenologic examination of the chest revealed bilateral pulmonary tuberculosis, with cavitation. The patient died in the Tuberculosis Division about three months after entry, without ever experiencing diarrhea.

Autopsy revealed an opening in the greater curvature of the stomach, about 5 mm. in diameter, which communicated with a sinus tract leading to a circular opening in the transverse colon. The sinus tract also communicated with two other openings into the colon, one into the transverse colon about 4 cm. from the first opening and the other into an ulcer in the cecum about 4 cm. above the ileocecal valve.

The absence of diarrhea in this case led us to study other gastrocolic and gastrojejunocolic fistulae in the records of the San Francisco Hospital. We were able to find the histories of six instances of gastrojejunocolic fistulae, all secondary to marginal or jejunal ulcers perforated into the transverse colon. These all occurred from two to 15 years after a gastro-enterostomy. In all of these patients, as in the three reported, the outstanding symptoms were diarrhea, and loss of weight and strength.

One of these patients had a gastro-enterostomy performed in 1915. He was well until 1923, eight years later, when he entered the University of California Hospital complaining of severe diarrhea and loss of weight and strength. A gastrojejunocolic fistula was demonstrated and repaired at operation by taking down the gastro-enterostomy and restoring the normal continuity of the bowel. The patient was well for one and one-half years when all of his original ulcer symptoms reappeared. Six months later he entered San Francisco Hospital complaining of pain in the abdomen and belching of foul-smelling gas. He had no diarrhea. Barium by mouth revealed a gastrocolic fistula. The small bowel was not involved. This patient had a gastrojejunocolic fistula at one time associated with a severe diarrhea and later a gastrocolic fistula with no diarrhea.

Six other cases of interest were reviewed. One case of rupture of a carcinoma of the stomach into the transverse colon, one carcinoma of the transverse colon into the stomach, and one gastrocolic fistula secondary to an abdominal abscess following trauma to the upper abdomen. In all of these cases a gastrocolic fistula was demonstrated roentgenologically, and in two, confirmed at autopsy. All three patients complained of belching of foul-smelling gas and of fecal vomiting; in none was a diarrhea present.

The other three cases reviewed, represented enterocolic fistulae; two carcinomata of the colon with rupture into the small bowel, and one carcinoma of the ileum ruptured into the large bowel. In all three of these patients, violent diarrhea was the outstanding symptom after the fistula had become established. In one patient the symptoms were those of a bowel obstruction

until the fistula appeared six days after entry into the hospital. Diarrhea was followed by relief of pain and vomiting.

Although diarrhea is said to be an outstanding symptom of gastrocolic fistula, a review of the cases reported in the literature would cast some doubt upon this contention. It is true that certain cases reviewed had diarrhea as an outstanding symptom but in most of these, the gastrocolic opening was very large or there was some obstruction to the normal flow of gastric contents through the pylorus. In a large number of the case histories reviewed, constipation rather than diarrhea was the rule. On the other hand, gastrojejunocolic fistulae and enterocolic fistulae in which a segment of small bowel is present and patent distal to the fistulae, diarrhea is invariably present.

These facts would tend to indicate that the low threshold of irritability of the small bowel has something to do with the development of diarrhea in these patients, and certainly tends to disprove the popular idea that the emptying of stomach contents into the large bowel is the etiologic factor. At any rate, there can be little doubt that short-circuiting the fecal stream, proximal to the fistulous opening, promptly alleviates all of the symptoms and restores the patient to normal health.

It is not the author's purpose here to discuss the choice of procedure after colostomy except to say that our review would indicate that simple restoration of continuity is frequently followed by return of the original ulcer symptoms and that simple closure of the colonic fistula is apt to lead to recurrence. Preliminary colostomy makes any subsequent procedure simpler and safer and, as indicated by the first three patients reported here, allows one to undertake extensive gastric resection.

SUMMARY

(1) Nine cases of gastrojejunocolic fistulae have been studied together with four cases of gastrocolic fistulae and three cases of enterocolic fistulae.

(2) Three cases of gastrojejunocolic fistulae treated by preliminary colostomy are presented in detail.

CONCLUSIONS

(1) Colostomy as a preliminary procedure in the treatment of gastrojejunocolic fistulae not only stops the diarrhea immediately and completely, allowing the patient to regain his body weight and normal fluid balance, but greatly facilitates the surgical correction of the fistula at a subsequent operation by correcting the inflammatory reaction usually seen about these fistulae.

(2) The diarrhea experienced in gastrojejunocolic fistulae is, definitely, the result of a reflux of colonic contents into the upper gastro-intestinal tract, rather than the influx of gastric contents into the large bowel.

(3) Diarrhea is a symptom of gastrojejunocolic fistula but not necessarily a symptom of gastrocolic fistula.

(4) Right-sided transverse colostomy, in our experience, is preferable to cecostomy in these patients.

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THE SURGICAL MANAGEMENT OF FECAL FISTULAE

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THE DEVELOPMENT of a fecal fistula following an abdominal operation is a source of great embarrassment to the surgeon and of considerable distress to the patient. This unfortunate complication is probably less common now than was once the case,[2] because of an increasing tendency to avoid operating for acute pelvic inflammatory conditions and because of a better understanding of such diseases as diverticulitis and regional enteritis. Yet it is still of sufficiently frequent occurrence to warrant an occasional appraisal of the methods employed in its management.

Recent progress in the care of patients having fistulae has been mainly in the field of conservative treatment. This phase of the problem has recently been reviewed by Dixon and Deuterman.[1] The main objectives of conservative treatment are to provide nature with every opportunity to bring about spontaneous healing, or, this failing, to get the patient into the best possible general condition before subjecting him to more heroic measures. Disturbances resulting from loss of fluids, electrolytes or enzymes, and nutritional deficiencies are recognized and corrected. Acute inflammatory processes are allowed to subside, and the condition of the tissues surrounding the fistula is improved as much as possible.

In this study we have attempted to evaluate the results of surgical treatment and to determine the factors influencing these results. As a basis for this study, the records of patients presenting themselves at the Mayo Clinic, between January 1, 1930, and December 31, 1934, inclusive, in whom an abnormal communication existed between the small or large intestine and the surface of the body, have been reviewed. Excluded were patients with anorectal fistulae or cases in which enteric stomata had been established purposely, in the course of stage-operations or for the relief of ileus.

It is generally stated that the greater the length of a fistulous tract, the greater the likelihood that spontaneous healing will take place. However, it is also true that the longer the tract, the greater the technical difficulties which may confront the surgeon, should operation prove necessary. This is well exemplified by the comparative simplicity attending repair of so-called "lip-fistulae"[3] (short tract fistulae in which continuity between skin and mucous membrane exists) in contrast to correction of the more complex fistulae of other types. One hundred and fifty-five cases of the latter were encountered in the five-year period embraced by this study. One hundred and twenty-eight of these patients were subjected to operation.

TABLE I

CAUSATION OF 155 FECAL FISTULAE

Underlying Disease Process or Condition for which Operation Was Performed	Cases in which Closure Was Carried Out at the Mayo Clinic	Cases in which no Operative Attempt at Closure Was Made at the Mayo Clinic
1. Appendiceal disease		
A. Appendicitis	36	8
B. Conditions resulting from appendicitis	5	1
2. Benign disease of the female pelvic organs	22	3
3. Tuberculosis (intestinal or pelvic)		
A. Definite	15	2
B. Questionable	3	4
4. Malignant tumors		
A. Intestinal	13	1
B. Pelvic	0	2
5. Inflammatory disease of the bowel		
A. Regional enteritis	11	0
B. Ulcerative colitis	4	0
C. Actinomycosis	0	1
6. Diverticulitis	6	3
7. Miscellaneous		
A. Obstructive conditions of the bowel	5	1
B. Intestinal perforation (gunshot, traumatic)	4	0
C. Affections of the spleen	2	0
D. External hernia	1	1
E. Cholecystitis	1	0

In Table I the fistulae are classified according to cause. Fistulae were most common following operations for appendicitis, appendiceal abscess, or conditions resulting from appendicitis (ileus, adhesions). Operations upon the female pelvic organs contributed the second largest number of fistulae. No fistulae occurred spontaneously, but in ten cases the only operation performed was drainage of an abscess secondary to rupture of an infected diverticulum, to perforation of an area of regional enteritis, or to pelvic inflammatory disease. There were no fistulae of congenital origin.

The operation which had resulted in the formation of a fistula was not a reliable criterion of the true nature of the underlying disease. Thus, of 67 cases in which appendicectomy had been performed, tuberculosis was found in seven, regional enteritis in four, malignant lesion in three, and diverticulitis in two.

In 11 cases fistulae had been present less than three months before the patient was admitted. In 26 cases the duration was between three and six months. The greatest number of fistulae (45) had been present between six months and one year. In 30 cases the duration was between one and two years; in 18, between two and five years. In 25 cases the fistulae had been present for more than five years. Included were one case of 45 years' duration, and three of more than 20 years' duration.

As would be expected from the preponderance of appendiceal disease as an etiologic factor, the right lower quadrant was the most common site of the external opening, with the low midline scar of previous pelvic operation occupying second place, and the left lower quadrant, third place. No portion of the abdomen, groins or loins escaped as a site of opening. In four cases fistulae existed in the wounds of posterior resection of the rectum, and in one

case fecal matter (and urine) drained from a perineal fistula. Multiple external openings were present in 21.9 per cent of the cases. The size of the opening was too small to admit a finger tip in the majority of the cases, but in almost one-fourth of the cases a larger opening existed. The most common type of drainage was a scant but unmistakable fecal discharge, while in about one-fourth of the cases which came to operation, between 25 and 75 per cent of the feces passed through the fistula. In four cases no fecal matter passed through the normal channels. In a few cases, only pus was discharged.

In 27 cases operative closure was not attempted, because of disinclination on the part of the patient, of some serious contraindication, or of a desire to allow further time for spontaneous healing. These cases will receive no further consideration in this study, and all references hereafter will be to the cases in which operation was performed.

The most common site of the internal opening was in the ileum, 40 cases (31.3 per cent). In 20 (48.8 per cent) of the postappendiceal cases, the opening was in the cecum or what remained of the appendix, but in 15 cases (36.6 per cent), in many of which secondary operations had been performed, the ileum was involved. In 39 cases (30.5 per cent) the sigmoid was the site of the internal opening, pelvic operations accounting for 40.0 per cent of these, diverticulitis for 17.1 per cent, and tuberculosis, regional enteritis, appendicitis and malignant lesions accounting for the remainder. The jejunum was involved in two cases, the ascending colon in one, the transverse colon in two, the splenic flexure in two (following operations upon the spleen), and the descending colon in three. In 25 cases the site of the internal opening was not accurately localized.

Single openings were found in 67 cases (52.3 per cent) and multiple openings in 36 cases (28.1 per cent). Additional complicating internal fistulae existed in a number of cases—enterocolic fistulae in two cases, enterovesical fistulae in four, and in two cases there were openings communicating with the vagina. The complexity of some of the fistulae was truly remarkable. In one case fistulae in the cecum, sigmoid and ileum opened into a common tract; in another there were holes in the sigmoid, transverse colon and cecum. In one case, in addition to multiple ileal fistulae, the sigmoid was found to be completely divided. Most of the complex fistulae occurred in cases in which there had been previous attempts at closure.

In a considerable number of cases it was possible, preoperatively, to establish fairly accurately the location of the internal opening. In five cases sigmoid openings were visualized proctoscopically. Injection of radiopaque substances into fistulae or administration of barium sulphate with subsequent roentgenologic study established the presence of fistulae in several doubtful cases, and the segment of bowel involved in many. Multiple internal openings were not well demonstrated by these methods. Roentgenologic study was most valuable in detecting underlying diseases of the bowel and in supplying information regarding the patency of the bowel distal to the fistula.

Many of the patients were very poor operative risks. Debility was most

marked in the cases in which there was colitis or regional enteritis, but it figured prominently in almost 20 per cent of the cases. Many of the patients were emaciated, anemic and bedridden at the time of admission. Marked excoriation of the skin or inflammation of the tissues surrounding the fistula was present in about 10 per cent of the cases. Partial intestinal obstruction existed in five cases. Pelvic abscesses were very common. Pulmonary tuberculosis was present in seven of the 18 cases of tuberculous origin. Intestinal parasites were discovered in three cases. Unrelated conditions, such as obesity, hypertension, nephrosis, diabetes, rheumatic endocarditis and neurologic disorders added to the risk in other cases. Previous operative attempts at closure, varying from simple extraperitoneal suture to complex resections, had been performed in 49 cases (38.3 per cent).

Preoperative preparation was carried out along the lines described by Dixon and Deuterman. Intraperitoneal vaccine was administered to a number of the patients, a practice since discontinued in such cases, in which there has obviously been ample autovaccination.

OPERATIVE PROCEDURES

Curettage and Packing.—This was carried out in 14 cases (10.9 per cent). Appendiceal, tuberculous, malignant and pelvic cases were represented in this group. When possible, multiple external openings were converted into single openings. In one case a foreign body was removed.

Extraperitoneal Closure.—Simple freeing of the stoma with inversion of the mucosa and closure of the skin, without entering the peritoneal cavity, was carried out in only five cases (3.9 per cent).

Intraperitoneal Closure.—This was the most commonly employed procedure, 47 cases (36.7 per cent). Diseased pelvic organs and appendixes, when present, were removed at the same time; abscesses were drained. In four cases short-circuiting operations, and in three cases proximal enterostomies were added for safety. In about one-fourth of the cases in which intraperitoneal closure was performed, such large defects in the wall of the bowel were present that simple closure by purse-string or transverse suture was not feasible and plastic procedures were required. Closure was usually effected with two or three layers of continuous catgut, silk occasionally serving in the outer layer. In most cases the abdomen was entered through the old incision, the fistulous tract being dissected out in the process, but in a few instances a new and remote incision, as recommended by Lockhart-Mummery,[4] was employed. Drains were left in the peritoneal cavity in about half of the cases. In the few instances in which the fistulous tract was not removed it was utilized for drainage, and in a few cases subcutaneous drains were employed. In the remainder, no drains were inserted.

Resection.—This was the second most commonly used procedure, 33 cases (25.8 per cent). It was the operation most frequently performed upon patients with regional enteritis or ulcerative colitis. Simple resection and anastomosis were performed in one-third of the cases in which this type of opera-

tion was carried out, while in another third, proximal enterostomy was added. In half of the remaining cases, stage resections were carried out, while in the remainder, leaking bowel stumps (left after previous resection) or previously short-circuited segments of bowel were removed. In a number of the cases repair of defects in other portions of the bowel was required.

Exteriorization.—Obstructive resection or simple exteriorization was performed in five cases (3.9 per cent), simultaneous closure of openings in other parts of the bowel being carried out in several cases. Subsequent closure of the operative stoma was performed in three of the five cases in this group.

Appendicectomy.—This was the only procedure carried out in four cases in which the fistula was ascribed to previous appendiceal disease.

Diversion Operations.—Fistula-bearing segments were short-circuited in three cases; in one case a previously short-circuited segment was further isolated by division of the bowel proximal to the fistula-bearing portion, and in six cases colostomy was performed proximal to the fistulous bowel.

Pelvic Operations.—Removal of pelvic organs affected by inflammatory disease was the operation performed in three cases, while in one case tuberculous pelvic organs were removed. In these cases either the opening in the bowel was not visualized or the condition of the surrounding tissues was felt not to warrant closure or resection.

Drainage of Intra-abdominal Abscess.—This was performed in three cases.

Exploration.—This was performed in three cases.

POSTOPERATIVE HISTORY

The average length of stay in the hospital of the 128 patients was 35 days. There were 13 postoperative deaths, a mortality rate of 10.2 per cent. In 28 cases (24.3 per cent of the 115 cases in which the patients lived) the wound was healed at the time the patient was discharged. In 60 cases (52.2 per cent of 115 cases) a seropurulent discharge persisted. In 27 cases (23.5 per cent of 115 cases) fecal matter was being discharged from the wound. Two of the healed wounds broke down after the patient left the hospital. Thirty-five of the wounds which were draining pus were subsequently reported healed, while four of those from which fecal matter was draining subsequently healed. There was no adequate follow-up on 23 patients (18.0 per cent of 128 cases), but in seven of these the wounds were healed at the time of discharge. A striking commentary on the seriousness of the condition is the fact that 16 more patients (12.5 per cent of 128 cases) died within one year of their departure.

Immediate postoperative complications included shock (seven cases), general peritonitis (ten cases), local peritonitis with abscess formation (five cases), severe wound infection (16 cases), erysipelas (one case), wound disruption (two cases), ileus (ten cases), pulmonary complications (ten cases), urinary fistulae (three cases), fecal fistulae (30 cases), external hemorrhage (one case), phlebitis (one case), and parotitis (one case).

An analysis of the 13 cases in which there were postoperative deaths re-

vealed that, preoperatively, three of the patients had partial intestinal obstruction, and five were recognized as poor risks because of debility or intercurrent disease. At operation, multiple internal openings or extensive defects in the bowel wall were found in nine cases. Extensive resections or plastic reconstructions were required in all but three cases. In one of these latter the patient was subjected to two extensive pelvic operations during a period of nine weeks; one was a severely debilitated patient suffering from ulcerative colitis, and the third died following closure of large and small bowel openings and removal of tuberculous pelvic organs. Postoperative shock occurred in five of the cases in which death occurred. General peritonitis was the cause of death in eight cases (associated with pneumonia in one case). Pelvic peritonitis was the cause in two cases (combined with pneumonia in one and with extensive ulcerative proctosigmoiditis in the other), shock and inanition in one case, bronchopneumonia in one case, and erysipelas in one case.

COMMENT.—Evaluation of the results of any given form of operative treatment was difficult because of the number of variables. The highest morbidity and mortality (18.2 per cent) rates accompanied resections. Yet these operations were carried out in the most difficult cases, in which the patients often were afflicted with other disease processes. Healing of the fistula was obtained in 51.9 per cent of those who survived resection. It is obviously unfair to compare these results with those following extraperitoneal closure, in which satisfactory results were obtained in four of five cases. Simple curettage was followed by healing in only six of 14 cases. Intraperitoneal closure, the most common procedure, was attended by a mortality rate of 10.6 per cent, and healing occurred in 64.3 per cent. The least satisfactory results followed the diversion operations, in most of which a second operation would have been required to effect a cure. Yet the safety of the procedure (no deaths in ten cases) warrants its use in certain cases, in a few of which healing will occur without further interference. The remaining operations were performed in too few cases to justify any conclusions, but, in general, it may be said that, although healing occasionally followed drainage of an abscess or the removal of diseased pelvic organs, results were not as a rule satisfactory when the internal opening was not closed.

We attempted to determine whether there was any difference in results following entry into the abdomen through the old incision or a new one, or following closure with or without drainage. We were unable to correlate results with any of these factors.

When the results were considered in relation to the cause of the fistulae, it was found that satisfactory results were obtained in about 60 per cent of the cases in which the fistula followed appendicitis or diverticulitis, and in the miscellaneous group. The least satisfactory results occurred in the tuberculous (31.3 per cent healed) and "malignant" (38.5 per cent healed) groups. Healing was obtained in 47.4 per cent of the patients whose fistulae followed pelvic operations, and in 53.8 per cent of the cases with regional enteritis. There were no deaths in the "malignant" group, chiefly because few extensive

procedures were carried out. The mortality was 4.8 per cent in the "appendicitis" group, 11.1 per cent in the "tuberculous" group, 13.3 per cent in the "regional enteritis" group, 13.6 per cent in the "pelvic" group, 16.7 per cent in the "diverticulitis" group, and 23.1 per cent in the miscellaneous group.

We were unable to correlate operative results with the duration of the fistula before operation.

SUMMARY

A review has been presented of 155 cases in which abnormal communications between the small or large bowel and the surface of the body existed. In 128 of these cases operation was performed, with a mortality rate of 10.2 per cent. Because of the risk and difficulty associated with operative interference, every opportunity should be provided to encourage spontaneous healing. The nature of the fistula and the reason for its persistence should be determined as accurately as possible before operation. There can be no standard method of operating upon fecal fistulae, each case presenting a distinct problem of variable complexity.

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THE LIVER GLYCOGEN AND LIPID CONCENTRATIONS FOLLOWING INTRAVENOUS GLUCOSE ADMINISTRATION AND DIET IN THE DOG* AND MAN† IN THE PRESENCE OF LIVER DAMAGE

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The intravenous method of administering glucose to surgical patients has become nearly universal and is frequently employed even when there is no contraindication to the ingestion of food by mouth. This is especially true in the preoperative preparation of the patient with extensive hepatic disease. In fact, Soskin[1] has recently stated that there is in these patients a "physiologic basis for intravenous glucose therapy," and has suggested that, with the intravenous method, more glycogen can be laid down in the injured liver than when carbohydrate is given by mouth. The widespread use by clinicians of the intravenous method of administering glucose would appear to indicate acceptance of Soskin's hypothesis. Evidence which we have obtained from the dog and man under a variety of dietary conditions leads us to question the validity of this concept.

The physiologic basis of intravenous glucose therapy, in the presence of hepatic damage, has been given by Soskin as follows: "A greater hyperglycemia is necessary to suppress the supply of blood sugar and to favor the deposition of glycogen in an acutely damaged liver than in a normal liver; however, when the blood sugar is raised to a sufficiently high level the damaged liver does respond like the normal, and ceases to supply blood sugar. The benefit derived from this limitation in the activity of the liver may be regarded as equivalent to the favorable therapeutic results obtained by limiting the activity of other damaged tissue and organs in order to facilitate repair . . . the fact that many toxic substances are excreted as glycuronates suggests that excess storage of carbohydrate favors detoxication."

Most of the patients with biliary tract disease, now receiving intravenous glucose therapy, have a component of chronic hepatic injury which is of long-standing, and a lesser or greater degree of acute injury which is conditioned, as a rule, by infection or by an obstruction of the common bile duct, either from stone or malignancy. There is considerable difference of opinion as to just how much damage a simple obstruction of the common bile duct can produce when previous hepatitis did not exist.

It has been generally agreed that the glycogen content of the liver in the

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† The work on man was aided by a grant from the United Fruit Co.

presence of bile duct obstruction is reduced.[2, 3] While the liver, acutely damaged by a variety of hepatotoxic agents, rapidly loses glycogen, there are no data now available which conclusively prove that under conditions of an adequate diet, considerable amounts of glycogen cannot be laid down in a subacutely or chronically injured liver.

It is now 27 years since Opie and Alford[4] published their experiments, which indicated that a carbohydrate diet protected the liver from injury by chloroform. Shortly thereafter Davis, Hall, and Whipple,[5] and Graham[6] confirmed these findings. In 1924, Moise and Smith[7] reported that the diets used by these investigators did not consist of purified foodstuffs and that they were inadequate for maintaining the weight of normal animals. These latter investigators found that a protein diet was more efficacious than a carbohydrate diet in protecting the liver from the effects of chloroform.

Clinicians have attempted to increase the glycogen content of the liver prior, and subsequent, to operation on the basis recently stated by Banks and Sears[8] that "abundance of hepatic glycogen forms the basis of the protective and regenerative action of high carbohydrate diets in liver necrosis." Evidence obtained in this laboratory,[9] and since confirmed by other investigators,[10] seriously questions the frequently repeated statement that glycogen *per se* plays a direct rôle in the protection of the liver from injury by chloroform.

We[12] have found that the addition of a sufficient amount of an adequate protein (casein) in the diet is the best method now available to reduce the degree and extent of the hepatic injury which follows the administration of certain hepatotoxic agents. Protein has a very marked lipotropic action and the reduction in the concentration of liver lipid which follows the ingestion of protein reduces the amount of the fat soluble hepatotoxic agents which can be held in the liver. More important, is our observation that certain proteins, or their split-products, offer direct protection against substances such as chloroform. Miller, Ross, and Whipple[11] have recently published data obtained in the dog, which suggest that "methionine and to a less extent cystine given by mouth or by vein 24 to 55 hours before anesthesia give a remarkable and almost complete protection to the protein-depleted dog against chloroform poisoning." Experiments recently conducted in our laboratory on the rat, fail to confirm these observations, in that, in this animal, methionine provided only a minor degree of protection.

Messinger and Hawkins[13] have extended our observations for they have shown that a high protein dietary protects the liver from arsphenamine necrosis, and Smith[14] has shown that such a diet protects the liver from selenium poisoning and sulfanilamide hepatitis.

Notwithstanding such clear-cut data, most clinicians must still agree with Banks and Sears,[8] for the intravenous injection of glucose still occupies an important place in the therapy of the patient with biliary tract disease, especially of a surgical character.

In this communication, we wish to present evidence from the dog that, even if glycogen storage is useful in protecting the liver from injury, such stores

cannot be maintained over periods of time by intravenous glucose therapy in amounts comparable to those commonly used in man. The data from man are given merely to demonstrate that, even in the presence of extensive injury, glycogen can be deposited in the liver and low concentrations of liver lipid can be obtained. The liver specimens were removed from patients undergoing operations for biliary tract disease under spinal anesthesia. We have been able to obtain these sections without in any way affecting the course of convalescence. The data demonstrate a similar relationship to that we have reported for the dog.[12]

Methods.—The dogs used in this study were growing mongrels, in a good general nutritional state, and weighing from 8 to 12 Kg., when the study was begun. Previous to operation they had been on a high fat diet for about two weeks. The diets and analytic methods have been described in previous papers.[9, 12]

The glucose was administered intravenously slowly as a 5 per cent solution, either twice or three times daily. Liver sections were removed for study approximately eight to ten hours after the completion of the last injection. In the animals fed by mouth, either voluntarily or by forced feeding, the last food was given the dogs approximately 17 hours before removing a section of the liver for study. The diets used in man varied considerably, due to individual desires of the patient. In addition to various foodstuffs, which were weighed before and after feeding, the patients received, at frequent intervals, banana-skim-milk-shakes reenforced with "Casec." A large portion of the additional protein was provided as cottage cheese.

Results.—Dogs which have been cholecystectomized, and whose common ducts have been ligated, so that no bile can flow into the intestine, rapidly lose their appetites. When such animals were offered food consisting of a mixture of table scraps or a synthetic diet, they ate from 25 to 125 Gm. per day (Table I). Upon such diets, in the amount ingested, the liver glycogen concentration decreased and the liver lipid concentration increased.

TABLE I

VOLUNTARY FEEDING—NO INTRAVENOUS GLUCOSE

Dog No.	Days	Initial Glycogen Gm. %	Final Glycogen Gm. %	Initial Fatty Acids Gm. %	Final Fatty Acids Gm. %	Dogs Ate Gm.-Daily
141	8	..	0.2	..	11.8	50–60
123	8	..	0.3	..	49.2	25–50
142	14	..	0.52	..	13.5	50–80
85	7	3.14	2.90	15.7	20.9	75–105
21	7	1.80	1.79	18.2	27.2	55–125
22	7	2.15	1.75	14.3	17.4	60–110
826	7	0.63	0.83	37.73	22.80	30–60
828	7	3.02	1.09	9.17	17.17	25–60
Average		2.15	1.18	19.02	22.49	

When, to similar animals, fed on similar diets, a 5 per cent solution of glucose was administered intravenously in amounts of at least 50 cc. per Kg.

of body weight, the original mean glycogen concentration was maintained and the lipid concentration decreased by approximately 20 per cent (Table II).

TABLE II

VOLUNTARY FEEDING PLUS INTRAVENOUS GLUCOSE

Dog No.	Days	Initial Glycogen Gm. %	Final Glycogen Gm. %	Initial Fatty Acids Gm. %	Final Fatty Acids Gm. %	Dogs Ate Gm.-daily
53	14	3.1	2.8	11.5	14.8	30–60
54	14	4.4	3.7	9.4	11.3	30–60
27	10	2.4	3.9	52.2	44.4	30–60
122	5	0.91	2.34	25.45	13.30	55–155
223	5	0.82	2.62	19.10	14.98	55–180
257	5	1.78	2.60	17.25	26.10	80–125
226	5	2.09	1.82	22.10	14.28	50–75
12	7	1.44	1.41	15.3	14.3	30–50
647	7	2.23	2.23	21.6	13.25	50–100
539	7	3.69	2.06	32.20	12.44	25–100
641	7	1.66	1.55	55.80	47.00	35–50
Average		2.23	2.46	25.63	20.56	

In a third group of dogs appetite was stimulated by the administration of thiamin chloride, and desiccated bile was administered by mouth. These dogs ate from 60 to 405 Gm. of the diet each day and, in addition, received 50 cc. of a 5 per cent solution of glucose intravenously. In such dogs the mean increase in liver glycogen was 84 per cent, and the liver lipid decreased approximately 20 per cent (Table III).

TABLE III

GOOD APPETITE PLUS INTRAVENOUS GLUCOSE

Dog No.	Days	Initial Glycogen Gm. %	Final Glycogen Gm. %	Initial Fatty Acids Gm. %	Final Fatty Acids Gm. %	Dogs Ate Gm.-daily
81	12	1.03	6.1	40.8	15.7	80–230
86	14	2.20	3.80	28.0	15.2	80–190
88	11	2.50	3.90	28.0	14.9	80–130
104	14	2.50	6.30	16.0	13.9	80–255
105	14	2.60	7.10	16.7	28.2	80–205
22	10	1.6	6.3	22.7	9.2	85–130
24	10	2.1	5.4	49.0	14.6	105–130
48	14	4.9	8.2	13.9	7.7	230–400
107	12	3.1	7.6	26.6	16.3	80–405
648	7	3.05	3.04	27.4	11.5	75–200
675	7	1.32	3.84	24.4	17.2	90–255
534	7	2.36	3.96	15.55	16.3	150–185
642	7	1.9	3.4	12.42	9.21	100–205
438	7	2.27	3.2	57.7	34.2	150–200
304	7	2.73	4.58	21.20	9.40	85–180
310	7	4.07	4.20	17.40	11.68	85–130
305	7	2.36	1.08	19.65	16.25	65–130
303	7	2.94	3.42	14.25	9.25	80–135
309	7	3.39	4.34	25.65	19.28	80–180
Average		2.57	4.72	25.12	19.49	

When forced feeding was instituted, the situation was even more striking. The dogs, whose data are given in Table IV, were fed with a carbohydrate-protein mixture consisting of 80 per cent of the calories as a carbohydrate, and 20 per cent of the calories as protein (casein). No glucose was given

intravenously, but the dogs received approximately 88 calories per Kg. of body weight per day. The mean increase in the concentration of liver glycogen was 236 per cent, and the decrease in liver lipid 73 per cent.

TABLE IV

FORCED FEEDING—NO INTRAVENOUS GLUCOSE*

Dog No.	Days	Initial Glycogen Gm. %	Final Glycogen Gm. %	Initial Fatty Acids Gm. %	Final Fatty Acids Gm. %
112	14	..	4.08	..	12.1
40	7	2.4	14.9	11.1	4.8
78	7	1.1	7.0	48.7	27.8
31	7	1.4	11.4	16.4	7.0
33	7	1.5	7.4	27.1	11.0
35	7	3.3	8.3	10.3	7.4
36	7	1.4	3.6	16.8	23.7
39	7	2.1	12.0	19.8	9.9
821	7	2.8	4.97	38.3	18.8
48	14	4.9	8.2	13.9	7.7
Average		2.3	7.77	22.5	13.0

* Eighty-eight calories per Kg. per day.

In contradistinction to data, such as these, are those obtained when similarly prepared dogs were given glucose intravenously, without any food by mouth (Table V). Such animals were given 50 cc. of a 5 per cent solution of glucose per Kg. of body weight, or more, during each 24 hours. In such animals, the glycogen concentration decreased by 50 per cent and the liver lipid concentration remained unchanged.

TABLE V

INTRAVENOUS GLUCOSE ONLY*

Dog No.	Days	Initial Glycogen Gm. %	Final Glycogen Gm. %	Initial Fatty Acids Gm. %	Final Fatty Acids Gm. %
22	7	2.13	1.75	14.3	17.4
50	8	1.8	0.2	22.1	20.8
178	5	1.21	2.90	40.52	42.75
224	5	1.53	0.39	53.85	33.30
172	8	1.80	2.38	14.88	15.06
175	8	1.23	0.50	13.34	16.30
307	7	4.59	0.42	19.27	24.08
176	5	1.31	0.45	47.40	41.02
312	7	2.06	0.93	17.77	14.14
817	7	1.40	0.06	34.95	24.30
14	7	0.96	0.08	22.7	28.10
15	7	1.61	0.54	12.8	16.00
643	7	2.06	0.62	11.81	15.20
672	7	0.11	1.18	57.8	46.20
673	7	2.11	1.25	20.10	16.40
674	7	1.68	0.63	27.4	17.20
528	7	2.15	1.86	12.77	19.17
532	7	2.44	0.21	11.07	13.24
441	7	0.53	0.9	23.9	48.8
443	7	2.54	0.66	11.4	32.9
447	7	2.38	0.45	14.2	30.4
448	7	2.93	1.3	14.6	20.6
449	7	0.94	0.63	14.8	15.3
Average		1.78	0.88	23.21	24.29

* 50 cc. of 5 per cent solution of glucose per Kg. of body weight.

In Table VI are given some data on the concentration of glycogen and lipid in the liver of man with biliary tract disease, at the time of celiotomy, under spinal anesthesia. They demonstrate that an adequate diet in man, for at least one week prior to operation, conditions the composition of the liver. In no instance have we found a high lipid concentration of the liver following what we have considered an adequate feeding period.

TABLE VI

				Immediate Operation (Within 3 days of Admission)					5 Days or More Preoperative. Diet of 2500 Calories or More—20% P, 6% F.				
Disease Duration	Prehosp. Diet	Prehosp. Appetite	Weight	Pt.	Sex	Liver Pathology	Fatty Acid %	Glycogen %	Pt.	Sex	Liver Pathology	Fatty Acid %	Glycogen %
Chronic	Low fat	Moderate	Obese	Sh.	F.	Chronic hepatitis. Marked fatty infiltration	11.8	2.9	Br.	F.	Chronic hepatitis, with cirrhosis	2.9	3.4
Common duct obstruction	Low fat	Hearty	Obese	Tr.	F.	Chronic hepatitis. Extensive fatty infiltration	15.4	2.9	Sk.	F.	Chronic hepatitis, with cirrhosis	3.7	6.7
Acute—3 mos.	Low fat	Moderate	Obese	Sc.	M.	Extensive chronic hepatitis, with fatty infiltration	7.9	2.2	Sk.	M.	Chronic hepatitis, with cirrhosis	3.4	3.1
Chronic—2 yrs.	Unrestricted	Hearty	Obese	Bu.	F.	Chronic hepatitis, with very extensive fatty infiltration	11.0	3.1	Ki.	F.	Chronic hepatitis, with mild cirrhosis	4.1	3.2

Discussion.—The data, presented in this communication, strongly support the concept that the amount of glycogen present in the liver, at any given period, depends to a large extent upon the amount of carbohydrate, or carbohydrate-forming substances available to the animal or patient. If, as we doubt, any great virtue, in itself, lies in obtaining a high concentration of hepatic glycogen, this can be obtained only by supplying a sufficient number of calories during the period of therapy.

The increasing tendency to place more and more emphasis on the greater value of intravenously injected glucose is fraught with the gravest of danger, for, as this is done, less emphasis is placed upon the administration of foodstuffs by mouth. It can be stated, with considerable confidence, that unless more calories are provided than are necessary to meet the energy requirements of the animal, or man, by diet or intravenous therapy, glycogen or protein will not be laid down in the liver.

It is impossible to supply sufficient calories for the energy requirements of man by any method of intravenous therapy now available. The usual program in this country is to administer to these patients 3,000 cc. of a 5 per cent solution of glucose every 24 hours. This provides but 600 calories from an

exogenous source, less than one-third of those needed by these patients for simple energy requirements. Even if the concentration is doubled, and this cannot be done for long periods, because thrombosis of veins occurs more readily and the renal spilling of glucose is encouraged, the caloric intake is still below that necessary to prevent extensive tissue destruction. Under such circumstances, foodstuffs cannot be more than temporarily stored in the liver for they must again be mobilized rapidly to meet the metabolic demands of the body.

A program of this type will constantly result in a demand upon the patient's tissues in order that the energy requirements of the patient be met. Such a circumstance regularly occurs in most hospitals, and the loss of weight which nearly every one of these patients undergoes is an expression of the extent to which food intake has failed to meet the energy requirements.

If the premises advanced by Goldschmidt, Vars, and Ravdin[9] are correct, the value of adequate protein in diet in the prevention of liver injury should rapidly be recognized. Not only does adequate protein in the diet protect the liver from a variety of hepatotoxic agents through some inherent properties of the foodstuff itself, but as Johnson, Ravdin, Vars, and Zintel[12] have shown, protein is more efficient in the presence of ductal obstruction in reducing the concentration of hepatic lipid than is carbohydrate. Finally, if repair is to be facilitated, protein must be available, for regeneration cannot readily take place on carbohydrate alone, especially when the protein stores of the body have been depleted by undernutrition. When repair does take place, following intravenous glucose therapy, the tissues of the body must supply the protein necessary for cellular regeneration.

The data of Banks and Sears[8] suggest that when equivalent amounts of glucose are given by mouth and intravenously, glucose "was slightly more efficacious by vein than by mouth in raising the glycogen content of the liver in dogs with obstructive jaundice." They pointed out, however, that "a caloric intake consisting entirely of dextrose and adequate to meet the daily energy requirements of the dog, was less productive of hepatic glycogen than a general diet with supplementary dextrose therapy."

It is our belief that adequate amounts of glucose, administered just prior to operation, may, in part, be deposited in the liver, but that such glucose will neither protect the liver from injury nor facilitate repair. Only by a fuller knowledge of the energy requirements of man, of the foodstuffs essential to meet these, and of the part which they may play in conditioning injury and promoting repair, can we prepare patients with hepatic injury satisfactorily for operation and convalescence.

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TORSION OF THE GREAT OMENTUM*

REPORT OF TWO CASES

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TORSION, or twisting of the omentum on its long axis, has been recognized for a long time as a rare clinical entity although the diagnosis of this condition has seldom been made before operation.

Aimes[1] credited Marchette with the report of the first case of torsion of the omentum, in 1851; Oberst,[19] however, was the first to record this condition, in 1882. Demons[6] reported another case, in 1893. In each of these two cases, a right inguinal hernia acted as a predisposing factor. Eitel[9] (1899) was the first to report a case of omental torsion unassociated with a hernia. Since that time many reports have appeared in the literature, notably that by Corner and Pinches,[5] which collated 54 cases up to 1905 (including three of their own), and that by Morris,[17] in 1932, in which 161 authentic cases of torsion of the omentum, from 1905 to 1930, were compiled, and three personal cases were added. His own series and that of Corner and Pinches permitted Morris to make careful analysis of this condition. The results of this study show that, while torsion of the omentum may occur at any age, it occurs most frequently between the ages of 30 and 50 (83 cases, 52.5 per cent); that males are more commonly affected than females in a ratio of two to one, and that the condition is associated with inguinal hernia (89 per cent in Corner and Pinches's series, and 50.3 per cent in Morris's). The analysis of Morris's cases further emphasized the facts that the herniae were of the right inguinal variety, were scrotal in type, of long duration, easily reducible, and that they almost invariably contained omentum.

McWhorter,[16] in 1928, reported 26 cases (including two of his own) of torsion of the omentum of the so-called idiopathic type, that is, cases arising within the peritoneal cavity, not associated with hernia, in which the causative factors were obscure.

The series reported here consists of the 16 cases reported in sufficient detail for analysis, since 1932, with two additional cases not previously reported (Farr and Bachman).

The classification offered by Morris is simple, though comprehensive, and facilitates the study and understanding of this condition:

(A) Complete Torsion:
  (1) Acute torsion with hernia
    (a) Hernial
    (b) Hernial and abdominal (combined)

(2) Acute torsion without hernia (purely abdominal)
  (a) Primary or idiopathic (unipolar)
  (b) Secondary (unipolar and bipolar)

(B) Incomplete Torsion:
  (1) With hernia
    (a) Hernial
    (b) Combined
  (2) Without hernia
    (a) Primary
    (b) Secondary

Farr and Bachman[11]	7 cases	Lucca[15]	2 cases
Bergquist[3]	2 cases	Barsky and Schwartz[2]	2 cases
Poling[21]	1 case	D'Errico[10]	2 cases

Total 16

Under this classification, it is understood that the terms "complete" and "incomplete" refer to the degree of torsion, complete torsion signifying cases in which the twisting of the omentum on its axis has caused sufficient interference in circulation to produce evidence of strangulation in the affected part of the omentum.

It is claimed that incomplete torsion may be of the "recurring" type, and that it is a definite clinical entity which can be recognized as such. Patients suffering from recurring abdominal pain may have temporary twists of the omentum. The "omental ball" and the omental fibrotic thickenings occasionally found, result from these recurring attacks of incomplete torsion of the omentum. The chronic changes occasionally found in the omentum in acute omental torsions seem to substantiate the occurrence of the recurring type of incomplete torsion. The case reported by Barsky and Schwartz,[2] for example, points strongly toward this possibility. A child, five years of age, had a history of frequent "colic" and, at operation for acute torsion, the omentum showed definite fibrotic changes.

Most cases of torsion are associated with hernia; a certain number, however, are caused by inflammatory foci within the abdominal cavity, which produce an inflammation in the neighboring omentum by contiguity. This may be true in cases of mild or subsiding appendicitis or cholecystitis in which the original focus subsides, but the changes induced in the omentum persist. The presence of a hernia containing omentum may eventually produce changes in the latter by means of constrictions or twisting of the pedicle in the neck of the hernia causing thickenings in the portion of the omentum within the sac. Thus a pathologic locus in the omentum is instituted.

Etiologic factors of torsion have also been traced by some (Robinson[22]), to the function ascribed to the omentum, that of "the policeman of the belly." It has been assumed by many that the omentum plugs up a perforation in a hollow viscus, and wraps itself around or attaches itself to an inflammatory focus in an attempt to wall-off the rest of the peritoneal cavity. This view

was flatly contradicted by the studies of Draper and Johnson,[7,8] whose critical review of the literature and of experiments conducted to clear up these points led them to believe that the only function of the omentum is bactericidal and absorptive, and that it possesses no automotive or ameboid characteristics of negative or positive chemotaxis.

According to Draper and Johnson, only in the quadruped has the omentum any definite function. It serves as a fat pad between the viscera and the hard abdominal muscles, and as a storage place for fat during the lush feeding period. In man, it is a vestigial organ, variable in size and shape. Some persons have an omentum so small that it is hard to conceive its possessing any function at all. Any apparent protective powers displayed by the omentum are purely accidental in nature. The author is inclined to accept this view for, were the omentum to possess a function, it would gain a more definite place in pathology. Pathologic conditions of the omentum are comparatively rare and are associated in the great majority of cases with inguinal hernia or some other intra-abdominal pathologic change.

The more acceptable predisposing causes, in the idiopathic type of torsion, are anatomic and physiologic in nature. The omentum is variable in size and deposition of fat. It may be in the form of an apron, with irregular deposits of fat, or may be composed of several fat-laden strings. The right side of this structure is usually lower than the left and may reach into the pelvis. There may be accessory omental lobules of moderate size attached to the border of the main omentum.

In addition to being the seat of more frequent pathologic processes, the lower right quadrant is also the place of greater physiologic activity; intestinal peristalsis and changes in intra-abdominal pressure tend toward the right side. This seems to be borne out by the significant findings of Bernstein[4]: "That, in spite of ovarian tumors occurring with almost equal frequency on both sides, yet torsion of these is twice as frequent on the right as on the left side." This impression is further strengthened by the fact that almost all cases of torsion are found in the right half of the abdomen, especially in the lower right quadrant.

Payr[20] offered another explanation for the occurrence of the abdominal type of torsion on the basis of the fact that the omental veins are more tortuous and more easily compressed than the arteries. According to him, engorgement of the tortuous veins may cause a partial or complete torsion of the omentum. Other factors then enter—the degree of twist, interference with the circulation beyond it, the anatomy of the omentum, or possibly a pathologic condition of the omentum itself. Recovery may ensue or the process may go on to complete atrophy or gangrene. Cases have been reported in which the omental tumor thus produced, became parasitic through its attachment to other viscera.[13]

Contributory factors mentioned in the literature, such as trauma to the abdominal wall, coughing, efforts at lifting, bicycle racing, hard labor, inges-

tion of heavy meals, violent purgation, or the taxis of hernia, probably act to complete an existing process of incomplete torsion. The conclusion may reasonably be reached that, in the greatest percentage of cases associated with hernia, the easily reducible portion of the omentum within a hernial sac undergoes inflammatory changes, the pedicle is gradually thinned-out and the repeated traveling of the herniated portion of the omentum in and out of the sac leads to torsion, incomplete until some sudden physical effort on the part of the patient influences factors within the abdomen to produce complete acute torsion. In two-thirds of the cases, the presence of a hernia is the predisposing cause.

According to Morris, the right side is more often affected because of these two factors: (1) The right side of the abdomen is the seat of more frequent pathologic processes; cholecystitis, gastric and duodenal ulcers, and especially appendicitis. (2) The omentum, lying in proximity to these, becomes secondarily involved and very often fixed to an inflammatory process. Thus an inflammatory condition favoring torsion is established in the omentum. If a point of fixation is produced, bipolar torsion may result.

It is more difficult to explain the idiopathic variety of torsion in which no discernible intra-abdominal conditions predisposing to torsion are found. The fact that torsion of the omentum has occurred in well-developed obese persons would lead one to suspect that the omentum was loaded with fat, the edge of the apron being more heavily laden than the rest, thus serving as a weight on a plumb-line, with the constant peristaltic action of the intestines favoring torsion. The rest of the mechanism has been discussed above. It is quite possible that venous tortuosity, as noted by Payr, is instrumental in initiating the process in these stout persons, causing mechanical changes in the omentum beyond a point of free lymphatic and venous circulation. One questions this mechanism as being the major cause in idiopathic torsion, for, were this factor alone operative, many more cases of intra-abdominal torsion would be recorded instead of 11 per cent in Corner and Pinches's series, 47.8 per cent in Morris's, and 87.8 per cent in this series of 18 cases. In the absence of function of the omentum, a likely explanation of idiopathic torsion is offered in the statement credited by Fuller[12] to Reidel, namely, that no torsion would occur were the omentum free from pathologic change. How this pathologic change in the omentum is produced still needs clarification. Perhaps the cause lies in internal hernial openings operating to produce an "omental ball," or changes in the omentum, produced by the intra-abdominal pathologic processes discussed above. These leave no gross evidence in the organ itself but give rise to sufficient alteration in the omentum to serve as the initial point for torsion under favorable circumstances.

A careful analysis of the 11 cases of the purely intra-abdominal type in this series, fails to reveal any explanation for the condition. It is true that in none of these were observations made seeking the cause. Morris's study also failed to bring forth any more definite explanation for this type of tor-

sion. The immediate causes for the torsion were ascribed to various physical efforts (dancing, lifting a heavy weight, *etc.*). Only two patients in this series gave a history of any possible antecedent cause; in one the torsion followed the ingestion of a hearty meal; in the other, it occurred while the patient was driving an automobile (Farr's case). The etiology of idiopathic torsion of the omentum is still obscure in spite of our greater clinical knowledge and better understanding of this condition.

REPORT OF TWO CASES

Case 1.*—C. S., a waiter, age 37, was admitted to the hospital, August 8, 1932, with the diagnosis of incarcerated hernia. The patient had had a right inguinal, reducible, scrotal hernia for 14 years. The hernia became irreducible on August 24, 1932 (four days prior to admission), and the patient developed symptoms of urgency and frequency of urination, soreness along Poupart's ligament, and swelling and induration of the right testicle. The patient had not had a bowel movement for the four days prior to admission but showed no signs or symptoms of intestinal obstruction.

Physical Examination.—The patient was a well-developed, well-nourished male. There was no tenderness or rigidity of the abdomen, and no abdominal masses were noted except a tender bulge, about 5 cm. from the right external inguinal ring to a point above Poupart's ligament. The right scrotum was filled with a sensitive mass, 3 cm. in diameter. The testicle was felt as a separate mass and was three times larger than the left. No varicocele or hydrocele was noted on either side. No diagnosis was made prior to operation.

Operation.—September 1, 1932: The sac was found to contain omentum only. The abdominal portion of the omentum was found to be gangrenous and twisted six times on its axis. The omentum was removed as high as the transverse colon. Following the operation, the patient developed paralytic ileus and bronchopneumonia, and expired September 5, 1932.

COMMENT.—This case comes under the classification of acute torsion, hernial and abdominal, bipolar.

Case 2.—J. G., a carpenter, age 36, was seen, December 18, 1936, because of an acute intra-abdominal condition. He had always been well and had had no previous operations. Three years previously, the patient had developed a right, incomplete inguinal hernia. He had been told at that time that he also had a large left inguinal ring. He had worn a truss for the three years and had no reappearance of the "lump" at the right external ring for the past two years, in spite of the fact that he had left off the truss on several occasions, for days at a time, while engaged in heavy work as a carpenter on construction jobs.

On December 16, 1936, after a heavy meal of corned beef and cabbage, the patient was awakened in the middle of the night by cramps in the upper abdominal region. He vomited a slight amount once, but the pain was not relieved. The patient slept comfortably the rest of the night but had chilly sensations in the morning. The upper abdominal pain became steady and dull in character. Attempts at eating resulted in an increase in the pain, without vomiting or nausea. In spite of the persistence of pain he had a full meal that evening and a hearty breakfast the next morning. During the next two days the pain recurred but was somewhat less when the patient lay down.

* This case was the only instance of torsion of the omentum which was recorded at the San Francisco Hospital, University of California Service, between the years 1919 and 1937. This is reported through the courtesy of Dr. Harold Brunn, Chief of the University of California Surgical Service at the San Francisco Hospital.

Sleep was disturbed during this period. On the third day, the pain shifted from the upper abdomen to the right lower quadrant, and all the tenderness and soreness in the upper abdomen disappeared. Sodium bicarbonate, by mouth, gave him no relief. An enema made him feel worse. At no time did he have any belching, distention or local tenderness.

Physical Examination.—The patient was a very robust, well-developed male, who looked chronically ill. The heart and lungs were normal. There was moderate rigidity of the entire right side of the abdomen, with tenderness to the right of the umbilicus and some slight rebound tenderness in the lower quadrant. No masses were felt in the abdomen or on rectal examination. The red cell count was normal. The white cell count was 6,500, with 87 per cent polymorphonuclear cells.

An exploratory celiotomy, with the possibility of acute appendicitis in mind, but with no diagnosis having been made, was performed December 19, 1936. The age of the patient, the blood count, and the entire course of the attack during the three days prior to the operation did not conform to any of clinical entities considered. Torsion of the omentum was not even thought of.

Operation.—A slightly injected appendix was found. The omentum consisted of flat semigangrenous tissue, two by three inches in size, suspended by a pedicle which was twisted on its axis five times. There was no free fluid. The mass was removed. Further exploration of the peritoneal cavity revealed no apparent cause for the torsion. The patient made an uneventful recovery.

COMMENT.—In spite of the history of hernia of the right side, we felt that it did not cause the torsion. The hernia was not of the complete reducible type. There had been no evidence of it for the two years prior to the occurrence of torsion. Yet the possibility that the hernia initiated the pathologic process in the omentum could not be ignored.

A comparison of the findings in three series of cases (Corner and Pinches, 53 cases; Morris, 164 cases; and the present study of 18 cases) is of interest. Our series bears out Morris's findings (in his own series and that of Corner and Pinches's) that torsion of the omentum occurs twice as frequently in men as it does in women. Inguinal hernia as the main etiologic factor, however, has lost its importance. It was considered to be the cause of torsion in 89 per cent of the cases reviewed by Corner and Pinches, and in 50.3 per cent of Morris's series, but in only 22.2 per cent of the present series. With more frequent and earlier attention to hernia, this type of torsion has diminished. The age at which torsion occurs has not changed materially. A history of previous symptoms suggesting the possibility of recurring torsion was present in 16 cases in the first series, 27 cases in the second, and in two in the present study. None was more than suggestive, but a history of sudden severe muscular effort, a sharp blow on the abdomen, an abrupt movement involving changes in intra-abdominal pressure, or a hearty meal, was present in a sufficient number of cases to point to these as exciting causes in torsion. The sudden onset of pain in the right side of the abdomen was a constant finding.

The differential diagnosis of acute torsion of the omentum, either hernial or idiopathic, is difficult and has seldom been made before operation. On the other hand, almost every variety of acute intra-abdominal condition has been mistaken for torsion—intestinal obstruction, tuberculosis of the cecum, torsion of the spermatic cord, perforated peptic ulcer, *etc.* There are, perhaps, more

suggestive diagnostic features in the hernial type than in the abdominal. According to Morris, the sequence of events in torsion associated with hernia is somewhat as follows: The patient, an obese man, of about middle age, who has had a reducible, complete, right inguinal hernia for a long time, suddenly —usually after severe muscular strain—finds the hernia irreducible. Pain and swelling appear in the hernial site. Nausea and vomiting are present, and an increase in pain develops. The pain gradually ascends into the abdomen and becomes localized in the right lower quadrant, or at the right side of the umbilicus. The patient's condition becomes progressively worse, abdominal rigidity and tenderness appear and a movable abdominal mass can be palpated. There is a slight elevation of temperature, and leukocytosis may be evident. The usual diagnosis is strangulated hernia, but the possibility of acute appendicitis cannot be ignored. At operation, gangrenous omentum is usually found in the hernial sac.

The abdominal, or idiopathic type of torsion, is even more baffling. Of the six abdominal cases reported by Corner and Pinches, five were diagnosed as acute appendicitis and one as suppurative omental hydatid cyst. These authors credit Lucas-Champonnière with the first reports of two cases correctly diagnosed before operation (1900, 1901). McWhorter, in a collection of 26 cases of the abdominal type, recorded no correct diagnosis, except Lucas-Champonnière's. Morris recorded only three correct diagnoses in cases of the idiopathic variety. In none of the present series was the correct diagnosis made before operation.

The simulation of acute appendicitis and acute cholecystitis, by torsion, is such that it is most often mistaken for one or the other of these conditions (over 75 per cent of cases of torsion were so diagnosed). The diagnosis of acute appendicitis was made twice as often as that of acute cholecystitis. This was especially true in the idiopathic type. The attempt by Smythe, Jeffries, and Mullen[23] to differentiate between torsion and acute appendicitis according to individual symptoms is not helpful. As pointed out by Morris, his largest series did not conform to the clinical picture of torsion as obtained by the foregoing authors. Morris, further, makes the point that no clinical symptom in appendicitis or torsion is specific. The present study tends to substantiate the opinion that it is almost impossible to differentiate torsion from acute appendicitis by means of a consideration of the rise in temperature, pulse rate, the blood count, or the presence of nausea and vomiting. A presumptive diagnosis of torsion may be made, however, when a robust man, in the third, fourth, or fifth decade of life, is suddenly seized with abdominal pain after a severe muscular effort or strain, and when, upon examination, a mobile mass is suspected or definitely felt to the right of the umbilicus. Mullen and Smythe attest the early appearance of such a mass, its mobility, its situation toward the midline, and the percussion of an area of resonance toward its one side. The fact was also emphasized that the symptoms in acute torsion are not so severe or so prostrating as they are in acute appendicitis. This explains the

longer delay in seeking medical attention. In the present series, the average interval between the onset of symptoms and surgery was two days.

One patient had had symptoms for two months. A diagnosis of acute cholecystitis was made but celiotomy disclosed a gangrenous omentum. Similar findings were present in a case of only a few hours' duration. The pathologic changes found at operation, such as hemorrhage or gangrene, depend on the degree of strangulation of the omentum. A serous or bloody exudate is present, and the presence of fluid may sometimes be elicited before operation. The finding of fibrotic changes in the involved portion of the omentum is indicative of a recurrent type. The number of twists (from three to 11) found in some of these cases is suggestive of a slow process of torsion, until the circulation of the omentum is compromised, when all the reflex phenomena express themselves as the symptoms described above.

Both Corner and Pinches, and Morris, stressed the possibility of a combined form of torsion in those cases in which the neck of the sac shows no constriction and the twisting extends into the abdomen. A herniocelotomy is necessary in these.

The various hypotheses as to the rôle played by anatomy and physiology of the omentum in the pathogenesis of torsion has already been considered. Very little actual information is recorded in the reports of cases of the abdominal type of torsion which might help in the understanding of the pathogenesis of this condition. Yet, a thorough exploration in these cases would probably discover possible causes for torsion. A plea is made for obtaining more complete data in the idiopathic type of torsion, noting especially the following:

(1) Hernial openings, external or internal, which might operate in the production of pathologic changes in the omentum.
(2) Inflammatory foci, acute, chronic or healed, which might explain initial changes in the omentum.
(3) Peculiarities in the anatomy of the omentum which might favor torsion.
(4) Other abnormalities which might serve to explain the occurrence of torsion.

Surgery is the only treatment. Recovery is the rule unless complications set in.

SUMMARY

(1) Sixteen cases of torsion are reviewed, and two additional cases are reported.

(2) An analysis of the hitherto reported cases is made.

(3) Emphasis is laid upon the increasing number of the idiopathic variety of torsion. Attention is called to the more common occurrence of torsion in the right half of the abdomen.

(4) Diagnostic points are stressed.

(5) A plea is made for more accurate observation and study of these cases.

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RIGHT PARADUODENAL HERNIA

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A paraduodenal hernia is a condition in which most of all the small intestine is incarcerated behind the folds of the mesocolon, making its entrance in the area of the duodenojejunal junction. This type of hernia comes under the classification of an internal or retroperitoneal hernia and comprises 53 per cent of all the internal herniae found. Two types occur: (1) Right paraduodenal hernia; and (2) left paraduodenal hernia. The latter is the more common, the ratio being about three to one. There have been 47 cases of right paraduodenal hernia reported, operation having been performed in 28 instances, with 15 recoveries.

The following conditions are usually found in a right paraduodenal hernia (Moynihan[19]): (1) The sac occupies the right half of the abdominal cavity, lying behind the ascending and transverse mesocolon; (2) the orifice is situated to the left of the sac; and (3) in the anterior margin of the sac, there lies either the superior mesenteric artery or a continuation of it, the ileocolic artery.

The case herewith reported is of interest because of its rarity and the unusual anatomic derangement associated with the hernia.

Case Report.—A female, age 49, was admitted to the hospital, September 17, 1939, complaining of vomiting, abdominal pain, and distention. The patient did not speak English and her history was obtained with difficulty through a Spanish interpreter. She stated that since the age of one year she had had "stomach trouble" consisting of attacks of abdominal pain with distention and occasional vomiting and diarrhea. These attacks were irregular but occurred at least once every three months. In 1929, she was told by a physician that she had an ulcer of the stomach. She followed a modified Sippy diet for a short time without improvement. She had observed that the severity and duration of the paroxysms were diminished on lying down. Every attack had been precipitated while she was on her feet. Food idiosyncrasies apparently had nothing to do with the onset of her periods of illness as she had been incapacitated at times when she had not eaten. September 1, 1939, the patient began having pain in the lower abdomen which soon radiated to her epigastrium and was accompanied by vomiting. This lasted six hours and was relieved following an enema. A diarrhea developed following this episode but rapidly subsided. The stools had a normal color. The patient had never menstruated, had been married 25 years, and had never been pregnant. She stated that she had had heart trouble, but the history of this was vague.

Three days before admission, September 14, 1939, the patient developed pain in her lower abdomen following the ingestion of some corn. The pain soon became generalized, and vomiting and distention of the abdomen became evident. Daily enemas did not produce fecal material and the symptoms persisted.

The relevant physical findings were obvious signs of dehydration, an oral temperature of 100° F., a blood pressure of 170/100, cardiac enlargement to the left, a distended and tympanitic abdomen, with exaggerated borborygmi, which could be auscultated over the entire abdomen, and generalized tenderness with rebound tenderness. All the labora-

tory findings were normal (blood count, Kline, and uranalysis). *Clinical Diagnosis:* Intestinal obstruction.

She was given intravenous fluids of glucose and normal saline, a Miller-Abbott tube was started, and a barium enema was given. The roentgenologic diagnosis, made by Dr. E. Hayden, was obstruction in the jejunum or proximal ileum, constriction of the midtransverse and sigmoid colon (Fig. 1), and apical tuberculosis was found by fluoroscopy. The patient's symptoms were not improved after eight hours of treatment, and it was thought advisable to explore the abdomen, as strangulation of the intestine was feared.

Operation.—Under cyclopropane anesthesia, a low midline incision was made. On opening the peritoneal cavity a confusing anomaly of the anatomy was found. No small intestine was to be seen. The transverse colon lay in the pelvis, attached by firm adhesions to the descending colon, the sigmoid, the peritoneum overlying the bladder and to the pelvic viscera. The adhesions between the transverse colon and the vesico-uterine peritoneum were cut to allow exploration of the pelvis. It was found that an infantile genital system existed. Superior to the transverse colon a mass could be palpated but not visualized. The incision was extended upward and around the umbilicus. At this point a mass could be seen which filled the upper portion of the abdomen. Intestines were seen to be enclosed in the tumor and it was recognized that a paraduodenal hernia was present. An attempt was made to find the opening leading into the sac but none was found. The hernial sac wall, consisting of the gastrocolic ligament and the mesentery of the ascending colon, was opened through an avascular area. The intestines were reduced through this opening; and it was found that the entire jejunum and greater portion of the ileum were contained in the hernial mass. There were several areas of purplish discoloration present in the bowel wall which recovered their normal color after reduction. By manually exploring the hernial cavity, the orifice was found to the left of the sac. This could be visualized only after adhesions between the transverse and descending colon were freed and the ptosed transverse colon retracted medially. The orifice was fully three inches in length, and the superior mesenteric artery traversed its anterior margin. The first portion of the jejunum entered the upper angle of the orifice into the hernial cavity and the distal end of the ileum emerged from the lower portion. By traction the intestine which had been incarcerated was pulled through the hernial orifice. Due to the length of the gastrocolic ligament, and the adhesions between the transverse colon and lower abdominal viscera, the position of the small intestines was still abnormal but ample room was afforded for them posterior to the gastrocolic ligament and superior to the transverse colon (Fig. 2). The hernial orifice was sutured with interrupted sutures of silk and the abdomen was closed in layers.

The patient's condition was good at the end of this procedure and continued so until the second postoperative day when signs of cardiac decompensation were observed. Digitalis was started followed by rapid improvement, after which the patient's recovery was uneventful. She was discharged from the hospital October 8, 1939, and has had no further signs of obstruction and no abdominal pain.

By reviewing the embryology of the intestine, the formation of a paraduodenal hernia can be better understood. The primitive gut arises in the human embryo when the entoderm is folded into a simple tube. This opens into the yolk stalk and is supported on the dorsal wall by the mesentery. During the fifth week the attachment of the yolk stalk disappears, the anlage of the cecum is formed, and there is a rapid elongation of the small intestine, which causes it to be thrown into a loop opposite the point of attachment of the yolk stalk. This loop rotates counterclockwise, and as a result the cecal

portion of the intestine lies to the left and the small intestine to the right (Plate I—Fig. 1). The small intestine continues to lengthen so rapidly that it can no longer be accommodated in the abdominal cavity, and, at seven weeks, it herniates into the umbilical coelom (Plate I—Fig. 2). The hind gut (major portion of the large intestine) is retained in the abdomen. In embryos of ten weeks the intestine returns into the abdominal cavity and the coelum is obliterated. The proximal coils of the small intestine are reduced first behind the superior mesenteric artery while the cecum returns last. As a result there occurs a counterclockwise rotation of 270° about the axis of the artery, throwing the duodenum behind and the transverse colon in front of the artery. Following the rotation the cecum lies to the right occupying a position immediately below the liver with the small intestines lying medially (Plate I—Fig. 3). In three- to six-months' fetuses the lengthening colon causes the cecum and cephalic end of the colon to descend toward the pelvis, and the ascending colon is thus established (Plate I—Fig. 4).

FIG. 1.—Roentgenogram of abdomen following barium enema showing dilated loops of small intestine and ptosis of transverse colon. The diagnosis of paraduodenal hernia could not be made from this film.

With the elongation of the intestines, the mesentery grows correspondingly and is carried with the intestine in its rotation. The superior mesenteric artery serves as the axis for the rotation. The axis is accentuated as the cecum descends and the mesentery is spread out like a funnel. During the fourth month the descending and ascending colons and their mesenteries fuse with the dorsal peritoneum (Plate I—Fig. 4).

The process just described is the normal development of the gut. Paraduodenal herniae are the result of an abnormal rotation of the intestine.

The formation of right paraduodenal herniae has been excellently described by Andrews,[1] and will be briefly reviewed. During the tenth week, when the intestine leaves the umbilical coelum, if an incomplete rotation of the cecum is present, this portion of the gut would lie inferior to the small intestines (Plate I—Fig. 5). As it grows to the right it would scoop up the small intestines in its mesentery (Plate I—Fig. 6), and when fusion occurs, during the fourth month (Plate I—Fig. 7), the small intestines would be imprisoned posterior to the mesentery.

The first paraduodenal hernia to be diagnosed preoperatively was reported in 1930, by Taylor.[23] Only two such diagnoses have been made, and these were made roentgenologically. A large number of patients with these herniae do not have symptoms and the anomaly is found at necropsy. In other cases

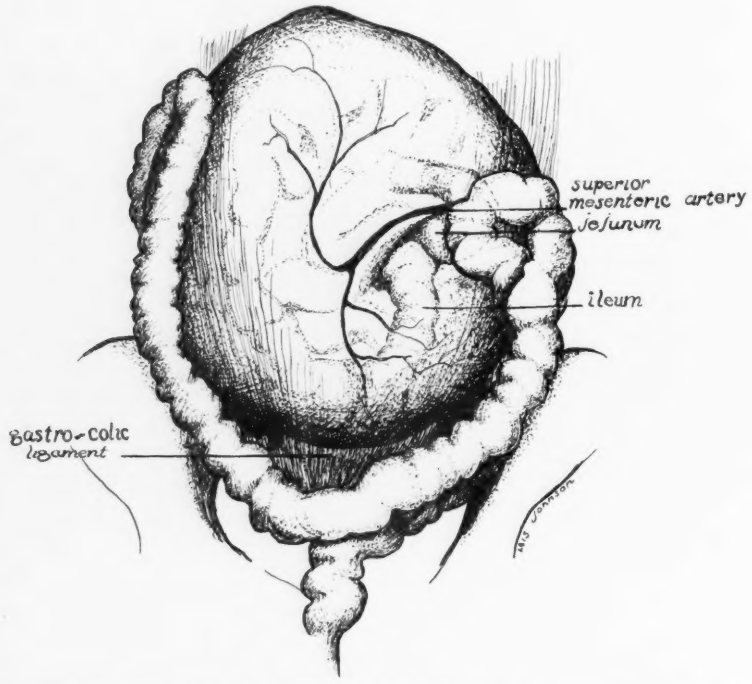

FIG. 2.—Drawing showing the anatomic relations found at operation. The paraduodenal hernia's anterior wall consisted of the mesentery of the transverse colon and gastrocolic ligament. The transverse colon lay inferior to the sac, and a portion of the colon overlapped the hernial orifice.

there are indefinite symptoms of colic-like abdominal discomfort which may be transient and with or without vomiting. The diagnosis of gallbladder disease, "dyspepsia," pyloric spasm, *etc.*, may be made. Again, there may be a sudden onset of symptoms indicating an acute intestinal obstruction. Bile is frequently present in the vomitus, but fecal vomiting is uncommon due to the usually high site of the obstruction. Moynihan[19] and Garber[11] both consider the chief diagnostic signs to be: Repeated attacks of abdominal colic; abdominal tenderness, with distention relieved by the passing of flatus; visible peristalsis; and a palpable, tympanitic, elastic mass in the abdomen. Scheele[21] claims that roentgenograms taken following a barium meal show retention in the stomach and duodenum, with a bow-shaped closing off of the upper intestinal shadow. A barium meal is contraindicated in cases with acute symptoms. Exner[8] states that the clumped appearance of the intestinal coils, shown in a "flat" roentgenogram, as if they were contained in a sac, is a characteristic sign of paraduodenal hernia. In large herniae, such as the

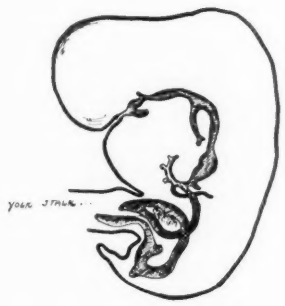

FIGURE 1

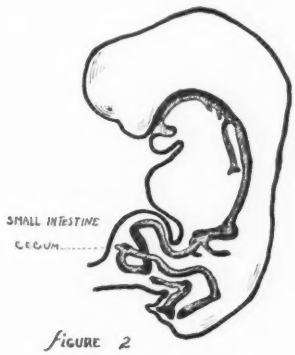

FIGURE 2

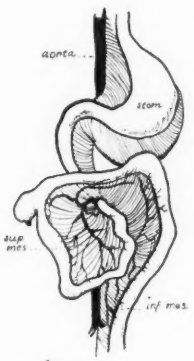

FIGURE 3

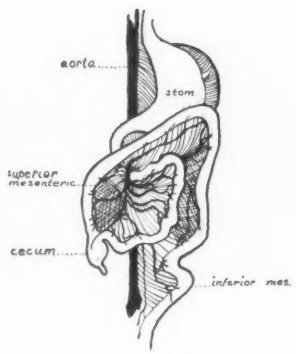

FIGURE 4

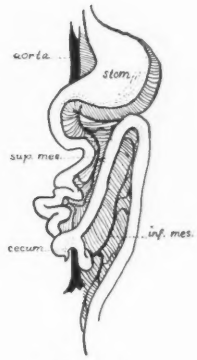

FIGURE 5

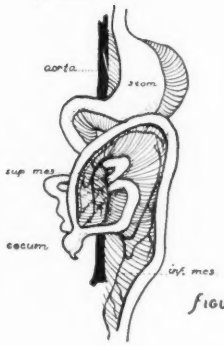

FIGURE 6

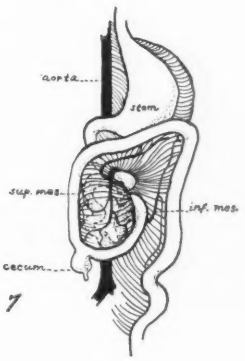

FIGURE 7

PLATE I

FIG. 1.—Diagrammatic fifth-week embryo showing counterclockwise rotation of the intestinal loop.

FIG. 2.—Seventh-week embryo with herniation of the small intestine into the umbilical coelom.

FIG. 3.—Position of large and small intestine following normal rotation in a ten-week embryo.

FIG. 4.—Normal rotation complete, with cecum in right lower aspect of the abdominal cavity. Shadowed areas represent areas of fusion between the mesenteries and the posterior peritoneum.

FIGS. 5 and 6.—Illustrating the relative positions of the large and small intestine when incomplete rotation occurs. The cecum lies inferior to the small intestine and as it grows to the right the small intestine is caught and enclosed in its mesentery. (After Andrews.[1])

FIG. 7.—In the fourth month the fusion of the mesentery and peritoneum has incarcerated the small intestine and completed the right paraduodenal hernia. Note that all conditions of the right paraduodenal hernia are reproduced; the sac and its contents occupy the right portion of the abdomen, the orifice is to the left of the sac, and the superior mesenteric artery lies in the anterior margin of the sac.

one described above, there is no roentgenographic evidence that the intestines are enclosed within a limited space.

The treatment advisable for this condition depends largely on the symptoms and findings present. Those herniae found in the course of the abdominal surgery should be reduced and the neck of the sac closed. When signs of an intestinal obstruction are present, the treatment should be the same as in any other case of obstruction. In cases with evidence of strangulation, surgery should not be delayed. If the hernial orifice cannot be located, an avascular area on the sac wall can be opened and the cavity explored manually. It was only by this method that the opening was found in the above described case. Caution must be exercised to protect the vital blood vessels which run in the wall of the sac. After the orifice is definitely located, the intestines can be drawn through the aperture into the general abdominal cavity and the opening closed. This last step is important as recurrences have been reported which resulted from an improper primary closure. "Because of the technical difficulties produced by the distortion of the anatomy, the mortality still remains high. This can be reduced only by a more thorough grasp on the part of the operating surgeon of the anatomic anomalies at hand" (Longacre[17]).

SUMMARY

A case of right paraduodenal hernia is presented which, as far as could be determined, is the forty-eighth case to be reported; the twenty-ninth case to be operated upon; and the sixteenth to recover. The anatomic arrangement found was interesting not only because of the hernia present but also because of the presence of an infantile genital system, and of the position of the colon in the pelvis. The cause of the generalized adhesions in the abdomen was not determined. It is logical to believe that they were a result of an old tuberculous peritonitis as they were of the right consistency and distribution. The presence of an apical tuberculosis adds further weight to the possibility of this etiology.

We wish to express our appreciation to Dr. W. Steen, who conducted the medical management of this case and was instrumental in obtaining the patient's history.

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MANAGEMENT OF VARICOSE VEINS OF THE LOWER EXTREMITIES

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VARICOSITIES of the lower extremities are as varied in distribution and size as there are individuals presenting them. From a therapeutic standpoint, however, they can be classified simply into three comparatively distinct groups (Table I):

TABLE I

CLASSIFICATION OF VARICOSITIES OF THE LOWER EXTREMITIES

	Condition	
Group	Varicosities	Great or Small Saphenous System
I.....	Spider bursts; rocket bursts; telangiectatic veins	Competent
II.....	Mild or moderate varicosities	Competent
III.....	Mild, moderate or marked varicosities	Incompetent

Group I.—To the first group are assigned the spider bursts, rocket bursts or the telangiectatic type of veins (Fig. 1). These are tiny, superficial, often interlacing vessels; complaints referable to them primarily concern their appearance. Occasionally, these vessels will rupture spontaneously. Somewhat more frequently, a sharp blow directly over the vein will produce a subcutaneous or external hemorrhage. Although not of serious import, such an accident causes considerable apprehension on the part of the patient. Elevation of the extremity affected plus external pressure over the region of hemorrhage will temporarily control the situation satisfactorily.

Group II.—To the second group are assigned mild or moderate varicosities that are not associated with demonstrable incompetency of the great or small saphenous system of which the varicose veins may or may not be a part (Fig. 2). If the varicosities seem to affect a portion of one or the other of the aforementioned systems, prognostication of permanent good results should be guarded, as recurrences frequently develop. This can be readily understood, for often this type of varicosity is a precursor to a general breakdown of the system involved.

Group III.—The third, and most common type of varicosity, is found in approximately 50 per cent of all the patients treated for varicose veins at the Mayo Clinic. This third group is made up of those cases of incompetency of the great or small saphenous system, or both, associated with mild, moderate, or marked varicosities (Fig. 3). Thus, these cases are found to be the most important, and the most exacting, with which we must deal, for it is in such

cases that we find the greatest percentage of complications of actual or potential stasis. Recurrence of varicosities due to previous inadequate obliterative therapy is also frequently noted.

General Examination Prior to Treatment.—No patient should be treated for varicose veins without a complete general examination. Its importance

Fig. 1. Fig. 2. Fig. 3.

FIG. 1.—Diffuse spider bursts that involve primarily the lateral aspect of the lower extremity.
FIG. 2.—Mild and moderate varicosities on the lateral aspect of the thigh over the anterior aspect of the knee and leg; the saphenous system is not involved.
FIG. 3.—Incompetent saphenous system with moderate varicosities. Note cirsoid dilatation of the saphenous vein at the fossa ovalis.

is emphasized, further, by the fact that patients who present themselves for this kind of therapy are commonly of that age-group in which early malignant disease has its greatest incidence. When malignant lesions or other pathologic conditions are found that demand early attention, treatment for varicose veins becomes of secondary importance, and may be carried out at a subsequent date. Numerous patients may be found to have conditions of minor importance which require treatment, although elective. If the patient's condition is otherwise satisfactory, such elective therapy may be carried out in conjunction with routine obliteration of the veins.

For those individuals who are found to have pathologic lesions of the pelvis or abdomen for which treatment is not urgent, it is frequently advantageous to obliterate the varicosities first in order to lessen the possibility of postoperative superficial thrombophlebitis or other vascular accidents.

When satisfied that the patient's general condition warrants obliterative therapy, it is inexcusable not to determine the status of the deep venous circulation of the lower extremity before proceeding further. This is especially true if one can elicit a history of a previous, deep thrombophlebitis.

In our experience, very few patients have significantly incompetent communicating veins of the thigh or leg. As yet, we have not found it necessary to ligate such veins for successful obliteration of the superficial system.

Test Dose.—To safely approach the obliteration of any type of varicosities, particularly those of the second and third group, a "test dose," or injection, should be given at least four hours, and preferably 24 hours, prior to therapy. We consider that 0.5 to 1 cc. of a 5 per cent solution of sodium morrhuate, or a like amount of 5 per cent solution of monoethanolamine oleate injected into a varicose vein of medium size, is the appropriate amount.

Systemic reactions seldom develop following the injection of endothelial irritants. However, if they should occur, the likelihood of minimal manifestations may be expected if small amounts are employed, as recommended for the test dose. Immediate administration of epinephrine hydrochloride has no peer in the control of these episodes. Obviously, before treatment is begun one must determine that the sclerosing solution to be employed is nontoxic to the patient.

The second important function of the test dose is to reveal information 24 hours after it is given. It is well recognized that sclerosing solutions do not react quantitatively the same among different individuals. Thus, the amount of local reaction produced at the site of injection of the test dose guides us in determining the amount of sclerosing solution to be employed at subsequent injections. This is particularly true in regard to the larger amounts used at the time of ligation and division of the incompetent vein.

Only after certain prerequisites have been fulfilled, namely, a satisfactorily general physical examination of the patient without evidence of disease of a serious nature and the selection of a nontoxic sclerosing solution, should treatment of the offending varicosities classified in Groups II and III be instituted.

Treatment.—Group I.—Small veins classified under Group I are obliterated primarily for cosmetic reasons. To accomplish this, infinite care must be employed to prevent further disfigurement which may easily occur if the sclerosing solution is not injected directly into the lumen of the vein. To minimize the danger of necrosis of the wall of the vein, which results in a highly pigmented scar, we use 1 to 2.5 per cent solutions of either of the previously mentioned salts of fatty acids. By vigorous shaking of the full strength solutions, surface bubbles are produced in the syringe. Injection of these bubbles may also be successfully employed to obliterate this type of varicosity (Group I).

Group II.—When dealing with varicosities of mild or moderate degree without associated incompetency of the great or small saphenous system, it is rarely difficult to produce a satisfactory result. Local injections of a solution of average strength usually suffice to thrombose adequately the offending

varicosities. We prefer to start at the proximal portion of the varices and proceed distally; we believe that when the proximal portion is thrombosed successfully, less solution is needed subsequently to obliterate the remaining patent portion of the vein. Treatments may be carried out daily, every other day, or twice weekly at the discretion of the operator. Although 2 cc. of a 5 per cent sclerosing solution is approximately the average amount employed in one day, it is seldom advisable to inject this quantity at a single site unless previous experience has proved otherwise.

Occasionally, it is permissible to use as much as 4 cc. daily, provided that the patient's tolerance is high, or that well-scattered sites have been chosen for the injections. The patient may be benefited by wearing an external support in the form of an elastic bandage during the course of injection and throughout the following few weeks. The advantages of a bandage are twofold: Adequate thrombosis is facilitated; and discomfort of the patient is lessened.

Group III.—Obliteration of varicosities classified in Groups I and II usually offers no difficulty if the described methods are employed. However, a much more extensive procedure must be instituted when the varicosities are of the type classified in Group III.

We believe that ligation and division of the offending incompetent vein, and injection of a sclerosing agent into it, must be meticulously performed to obtain the greatest percentage of permanent results. The advantages of such procedures are enumerated in Table II.

TABLE II

ADVANTAGES OF LIGATION OF INCOMPETENT GREAT SAPHENOUS VEIN

(1) Continuity of the vein is interrupted at its most proximal point.
(2) Possibility of canalization is reduced to a minimum.
(3) Number of local injections necessary for obliteration is decreased.
(4) Period of treatment is shortened.
(5) Adequate complete thrombosis is obtained with greater ease.
(6) Pulmonary showers are less likely to occur.

It should be emphasized, at this point, that during examination, while the patient is in the standing position, not only the proper diagnosis and classification can be ascertained but, also, unusual variations and distribution of the varicosities can be noted. Particularly is this true when groups of uncommon varices appear on the lateral or posterior aspects of the thighs. These indicate the presence of either incompetent lateral superficial femoral veins or incompetent medial superficial femoral veins (frequently termed accessory saphenous veins). When one or the other is present, it is important to identify it at operation. Treatment for such a condition is carried out simultaneously with that employed for an incompetent great saphenous vein; namely, ligation and division of the vein and the injection of a solution into its distal portion.

At the examination prior to operation, it is also of value to note regions either on the thigh or legs in which great tortuosity or a localized accumulation of varicosities occurs. To prevent an excessive localized reaction due to concentration of the sclerosing solution in these regions, and to procure uniform

thrombosis, binding of the thighs and the application of bandages to the legs are recommended to be used immediately following the operative procedure. The patient is advised that the binder may be removed from the thigh at any time after the lapse of a few hours. Removal of the binder may be necessary because of the considerable pain which, occasionally, may follow as the result of swelling from the underlying chemical phlebitis and periphlebitis. If there are no symptoms, the binder is allowed to remain in place until the patient is seen on the following day.

For the same reasons that a binder is applied to the thigh postoperatively, an elastic bandage is employed on the leg. The patient is instructed that the bandage may be removed whenever the extremities are elevated, that is, while in bed; the bandage should be reapplied when the patient is on his feet or in any position in which the feet are dependent. As we expect the patient to leave the hospital soon after the operative procedure is performed, it is advisable to warn him that nausea, anorexia, and a mild elevation of temperature may occur postoperatively. He is also informed that if pain, tenderness or redness occurs along the course of the treated vein, elevation of the extremity and the application of warm, moist packs will be very beneficial and will decrease his discomfort. The patient is asked to return to the clinic on the day after operation.

Technic of Division and Ligation; Technic of Injection of the Sclerosing Solution into an Incompetent Great Saphenous Vein.—The site of the fossa ovalis, and, consequently, of the saphenofemoral junction, is determined after the patient is on the operating table, and draped for the operation. The point of maximal pulsation of the femoral artery at the lower border of Poupart's ligament is determined. We then measure downward, approximately one inch (2.5 cm.), and then medial approximately one inch. A scratch mark is made on the skin at this site which, in the majority of instances, has proved to lie directly over the fossa ovalis. After the region has been infiltrated with a 1 per cent solution of procaine hydrochloride, an ample incision is made parallel to Poupart's ligament; the marked site of the fossa ovalis is used as the middle point of the incision. The incision is carried down to the superficial fascia and a self-retaining mastoid type of retractor is inserted.

The great saphenous vein lies beneath the superficial fascia and superficial to the fascia lata of the thigh. The superficial fascia is incised in a line parallel to that of the incision. Occasionally, blunt dissection is necessary to expose the vein when it is surrounded by excessive areolar tissue. The great saphenous vein is separated from its bed for a short distance and a curved clamp is passed beneath it.

The vein is doubly ligated with chromic catgut, and a curved forceps is placed on the vein just proximal to the ties. The vein is then divided between the ligature and the forceps, and the distal portion is allowed to retract downward.

The three uppermost tributaries of the great saphenous vein, namely, the superficial circumflex iliac; the superficial epigastric; and the external puden-

dal veins, can be exposed by making traction on the proximal stump of the great saphenous vein and, by carefully stripping from it, with the index finger, the surrounding loose areolar tissue as far proximally as the femoral vein. These three tributaries are divided and ligated separately—this leaves the proximal stump of the great saphenous vein free of all tributaries. Two other tributaries of the great saphenous vein, the lateral and medial superficial femoral veins, are, ordinarily, not visualized in this dissection at the fossa ovalis. Occasionally, however, when one or both of these veins enter the great saphenous vein at a level higher than usual, they will be seen. When this occurs, these tributaries are treated as the aforementioned tributaries were treated and, in addition, a sclerosing solution is injected into their distal stumps. When one, or both of these tributaries are present, this essential additional procedure can be anticipated by careful preoperative examination.

By traction on the freed proximal stump of the saphenous vein with the attached forceps, the anterior surface of the femoral vein is exposed and two curved clamps are placed at the saphenofemoral junction. The great saphenous vein is doubly ligated with chromic catgut just beneath these clamps. The excess portion of the stump is excised. The ligated distal portion of the great saphenous vein is pulled upward into the wound, and the predetermined amount of sclerosing solution is injected directly into the lumen. The wound is irrigated with a saline solution and is closed with interrupted sutures.

Postoperative Care.—The return of the patient to the clinic, on the day following operation, is requested, primarily, in order to assure him that he is still ambulatory. If the bandages are still on the thigh, they should be removed. If indicated, the dressings over the incision may be changed. This is occasionally necessary because of discomfort or inadequate protection. The elastic bandages on the legs are removed and are reapplied following a survey of the extent of the postoperative reaction.

The extent of the reaction is noted by inspection and gentle palpation. In most instances, the reaction extends to the level of the knee and is visible as a pink to red periphlebitis. Induration and tenderness in this region also indicate the extent of the thrombosis that has resulted. Occasionally, the reaction extends through the entire involved saphenous system; if such occurs, the necessity for subsequent injections is reduced to a minimum. In the majority of cases, however, subsequent injection of a sclerosing solution into the remaining patent varicosities must be carried out to complete the obliterative therapy. It is, usually, wise to postpone this additional treatment until the second or third postoperative day, as occasionally the maximal extent of the postoperative reaction is not obtained by the end of the first 24 hours. Should excessive periphlebitis occur during the early postoperative course, the symptoms may prevent the patient from being entirely ambulatory. When simultaneous bilateral procedures have been carried out, some increase in disability may be expected. If more than an average reaction occurs, it can be satisfactorily controlled by intermittent rest in bed, elevation of the ex-

tremity and the application of warm, moist packs. If necessary, sedatives may be administered for a short time.

Further therapy, in the form of injecting an additional sclerosing solution, now depends entirely on the judgment of the surgeon. It is usually preferable to obliterate the remaining patent varicosities by successive, frequent injections of small amounts of the sclerosing solution, proceeding distalward.

If the cutaneous edges of the wound have been accurately approximated, the sutures are removed on the sixth postoperative day. In an occasional case, it may be wise to allow the sutures to remain in place an additional 24 to 48 hours. No wound complications have been observed following ligation of the great saphenous vein or its tributaries. We have not considered the accumulation of serum as a complication. When present, adequate drainage allows rapid subcutaneous healing of the wound.

Instructions to Patient.—The patients treated for varicosities, who do not reside in the immediate vicinity of the Mayo Clinic, are usually instructed at the time of their dismissal in a special manner. A brief description of the purpose of the obliterative therapy, given to the patient at the onset of treatment, is repeated at the time of dismissal; this tends to bring about the cooperation and understanding that are necessary on the part of the patient. Soreness and tenderness of varying degrees are to be expected whenever satisfactory thrombosis has resulted in the obliterated varicosities. Usually, a period of a few days, to two or three weeks, is sufficient for most patients to accommodate themselves to these complaints. Further complaints referable to the hard, contracting, thrombosed varicosities, such as pulling, drawing or sticking sensations, stiffness, dull aches, etc., may continue for one or two months. In numerous instances, the hardness of these thrombosed veins, on palpation, continues for a year or longer, and is indicative of a satisfactory result. The patients, if forewarned, will in no way become alarmed when they first notice these hard masses. An elastic bandage, or some other suitable means of applying external support, is recommended. The length of time advised for continuing external supportive measures depends, in most instances, directly upon the extent of varicosities. The average individual will derive no benefit from such support after three or four weeks, whereas those patients who have had complications such as persistent edema of the leg, brawny induration, or ulceration may require the application of an external support for six months or a year, infrequently longer. In addition to the factor of comfort, external support is a definite aid to nature in rehabilitation of the extremity, particularly when varicosities or complications have been extensive.

The patient is further requested to return for observation, preferably six months to a year following dismissal. Frequently, at this time, a few additional varicosities or regions of recanalization may be detected. A small amount of sclerosing solution, strategically injected, will then usually permanently complete the obliterative process.

SUMMARY

From a therapeutic standpoint, varicosities of the lower extremities may be classified, simply, into three comparatively distinct groups: (1) Spider bursts, rocket bursts, telangiectatic veins; (2) mild or moderate varicosities without associated demonstrable incompetency of the great or small saphenous system; and (3) mild, moderate, or marked varicosities associated with incompetency of the great or small saphenous system or with incompetency of both systems. On the basis of this classification, our method of therapy depends, and has been described. Approximately 50 per cent of patients treated have demonstrable incompetency of the great saphenous system. In such cases, the essential steps in treatment are: (1) Ligation and division of the great saphenous vein at the saphenofemoral junction; (2) separate division and ligation of the tributaries of the saphenous vein; and (3) injection of a sclerosing solution into the saphenous system. Methods of preoperative and postoperative management are very important.

VISUALIZATION AND OBLITERATION OF ANGIOMATA BY RADIOPAQUE SOLUTIONS

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THE EMPLOYMENT of opaque substances to roentgenographically demonstrate hollow organs or human cavities has now become a routine procedure. While at first these media were introduced by ingestion, injection or instillation to visualize local parts, the development of nontoxic substances permitted their injection directly into the circulation in order to demonstrate remote parts. Originally, these chemicals were employed solely because of their radiopacity but as research in this field developed, newer drugs were utilized which, in addition, permitted studies of the excretory or secretory functions of the organs studied. Further investigation led to the use of substances such as thorotrast, which remain within the reticulo-endothelial system of solid organs and thus renders them opaque. Thus it is safe to say that few organs are inaccessible to roentgenographic study.

The use of opaque substances, to map vascular channels, has, hitherto, been restricted to specimens removed at autopsy, operation, or in animal experimentation. Its use *in vivo*, however, is of more recent origin and is made possible by the development of opaque substances which can be introduced into the circulation without untoward effect.

In a previous communication,[1] we demonstrated the morphologic changes which occurred in varicose veins, the character of the associated circulatory phenomena, and the existence of venous pools subjacent to varicose ulcers. A wholly fortuitous development was the sclerosing effect of the skiodan.

During the course of this investigation, we had occasion to inject several angiomata. The prompt subsidence of the tumors which followed this procedure, encouraged us to extend the study to include the plexiform and cavernous angiomata of the extremities, we refer particularly to the angiomata of muscles and not of bone; because the identification of the individual types is frequently impossible by all methods. By employing radiopaque substances such as are used in intravenous urography, we were, in effect combining several operations in one. The course and extent of the tumor could be visualized and recorded. No subsequent sclerosing media would be necessary, since vascular obliteration would frequently follow the introduction of these chemicals into the vessels. Our experience in this connection forms the basis for this communication.

Incidence.—Jenkins and Delaney[2] studied 255 cases of muscle angiomata reported in the literature, up to 1932, and added one case of their own. It is obvious from their work as well as from our own experiences that the condition is extremely common but frequently unsuspected. Because of their

excellent review of the subject, it would be repetitious to cover the same ground here. The distribution of the cases studied by these authors is seen in Table I.

TABLE I

AGE OF PATIENT AND AGE AT ONSET OF SYMPTOMS

	Given During	Given at Onset of Symptoms and Signs
First decade	40	95
Second decade	80	67
Third decade	63	30
Fourth decade	20	7
Fifth decade	9	4
Sixth decade	2	1
Seventh decade	1	1
Eighth decade	1	1
Total	216	206

The largest individual group, therefore, occurred during the second decade. Where the age of onset of the symptoms was given however, 95 cases occurred during the first decade.

Of the 204 cases in which the sex was stated, 107 were in females. The condition occurred chiefly in the white race as only six Japanese and one Negro were included in the series. We have found that vascular diseases are uncommon in the colored people, whereas angiomata occur relatively frequently. In our group, there was a slight preponderance of the condition in the colored race. From the figures submitted by these authors, it is hard to escape the conclusion that the condition is congenital in origin, since 47 per cent occurred during the first decade in their series and in two of our cases. That trauma may be of significance is evidenced by the 17 per cent which followed injury. Four of our own cases gave a definite history of injury.

Symptoms and Physical Findings.—It is difficult to diagnose this condition solely by the symptoms and physical findings. There is often a history of a slowly developing tumor, which was noted at birth or shortly thereafter. Pain is a prominent feature and is usually present but somewhat variable in character, lasting from a few minutes to a few days. Often, it may be excruciating and completely disable the patient. Pain may be present at the site of the tumor, or it may radiate down the lower extremity and resemble a sciatica. Aggravation is usually produced by walking and exercising, and relief may be obtained by any position of the extremity which tends to empty the vessels. One of our cases, however, experienced pain on standing and was relieved only by brisk walking or dancing. Trauma may cause a rupture of a vein or a localized thrombophlebitis and frequently directs the patient's attention to the tumor which has escaped his notice. The patient may develop a peculiar gait or limp due to an alteration in the length of the extremity or to direct involvement of the soft tissues. The muscles of the lower extremities are most frequently involved.

The tumor varies in size from a small nodule to an extremely large irregular mass, the size of a small orange or even larger. While its surface is usually smooth, it may at times be extremely irregular in contour or nodular. Occasionally, it is sharply defined, but more often its limits are lost in that of the neighboring muscle. The skin overlying the mass may be freely movable or attached. Port wine nevi are common and in three of our cases, dilated vessels were visible. Frequently these nevi were somewhat distant from the enlarged vascular loops. Two instances of unilateral hypertrophy of an extremity were encountered, in which vascular nevi and angiomatous dilatation of the vessels coexisted. At times, there may be an increase in the width of an extremity without any change in its length. In one of our cases, there was a slight retardation of growth of the extremity due to a mild residual poliomyelitis. In angiomata involving joint structures, there may be a marked atrophy of the contiguous soft tissues producing a fusiform swelling. Motion of a neighboring joint may be distinctly restricted or painful. In a reported case, as well as in one of our own, an anesthetic had to be administered in order to allow palpation of the tumor. In our protocols, it is described as having a spongy or rubbery consistency. Occasionally, one can feel a small nodule or an elongated area of painful induration or swelling due to a localized phlebitis which serves to direct attention to the associated angioma. Ulceration of the skin overlying the tumor has been reported.

Diagnosis.—Essentially, the roentgenographic demonstration of phleboliths in the muscles of an extremity is pathognomonic evidence of this disease; but it is important to remember that these tumors may exist without the presence of phleboliths. Occasionally, one may detect some calcification within a soft tissue tumor, or a periostitis of an adjacent bone resulting from the irritation produced by the presence of a soft tissue mass. The most accurate aid to diagnosis which we possess is the injection of a radiopaque substance in order to visualize and identify the lesion.

Technic of Administration.—A preliminary roentgenogram of the part is taken in order to establish whether or not there are any phleboliths. Any syringe and needle used in the injection treatment of varicose veins may be employed and from 5 to 20 cc. of a 40 per cent solution of the radiopaque chemical is sufficient for the study. The patients are prepared as for any intravenous medication. The use of the tourniquet is preferable, as some stasis of the dye in the tumor is desired. When we are assured that the needle is within the vessel, the chemical is injected slowly and without undue pressure. The limb is placed upon a casette-changing device and toward the end of the injection, roentgenograms are taken. The needle need not be removed between exposures since it serves as a guide to the site of injection and prevents the back flow of radiopaque chemical upon the skin, where its superimposed density often masks finer vascular changes. Should it become necessary, however, to remove the needle in order to rearrange the part, a

small metallic marker may be placed as a guide at the site of injection. It is obvious that the dilution of the chemical may be very considerable in tumors of large size, and it may be necessary at times to reinject it to obtain a thorough sclerosing effect. In some tumors, however, one injection is usually adequate for visualization and therapeutic action, and in only one instance was it necessary for us to inject more than twice. In properly obliterated angiomata, it will be impossible to introduce the radiopaque chemical into the mass. Care must be exercised during the injection to assure one's self that the chemical is introduced into the angioma and not into the tissues about it, as a bad slough may develop. In none of our patients was there any untoward effect. Small angiomata in children need not be injected since they may spontaneously retrogress without treatment.

CASE REPORTS

Case 1.—Hosp. No. 4577: L. P., male, age five, was admitted, September 7, 1933, on the service of Doctor Finkelstein for a painful ulcer and swelling of the right foot. The mother stated that at the time of birth it was noted that the child had a large, soft tissue tumor involving the entire plantar surface of the foot, extending from the base of the toes to but not involving the heel, as well as a swelling below the external malleolus. At the age of eight months, the patient was taken to an hospital, where, over a period of four months, he received two roentgen ray treatments and one radium treatment. A huge blister soon developed at the site of treatment, which was incised. Excruciating pain soon developed in the extremity. He was observed monthly until the age of three, at which time further radium treatment was advised but declined. In the absence of any therapeutic response, and because of the pain which required sedation to control, amputation was advised. For the past four weeks disability has been complete and the pain agonizing.

Physical Examination.—The patient was unable to walk or stand and the foot was held in the equinovarus position. There was a marked atrophy of the foot and calf. In the middle of the plantar surface of the foot, there was a large ulcerated area, measuring about one and one-quarter by one-half inches. From this area, radiating bands of scar tissue extended to the lateral borders of the foot. The ulcer was covered by an unhealthy crust which was rather firmly adherent to its somewhat edematous borders. The entire plantar surface of the foot consisted of irregular clumps of enlarged tortuous veins which extended from the base of the toes practically to the heel. The skin over these veins was extremely thin and somewhat bluish in color. On palpation the vessels were found to be of somewhat rubbery consistency and painful. The dorsum of the foot was likewise swollen (Fig. 1).

The preliminary roentgenogram showed a fairly pronounced swelling of the foot. Nodular, soft tissue masses extended from the bases of the toes to the heel. On the plantar surface and somewhat centrally placed, there was a loss of soft tissue substance, representing a fairly large ulcer. Close to it and below the base of the fifth metatarsal bone, a small phlebolith was noted. On the internal surface of the fifth metatarsal bone, there was a crescentic filling defect, which extended from the base of the head of this bone, materially reducing its diameter. This was evidently due to the pressure of a soft tissue mass. On the surface of the shafts of the third and fourth metatarsal bones, a parallel periostitis was noted (Fig. 2).

Because of the phlebolith, the lesion was considered an angioma, and it was decided to inject an opaque solution for diagnostic and sclerosing purposes. Under a general

anesthetic, 10 cc. of skiodan was injected into the plexus of veins in the region of the base of the third metatarsal bone and roentgenograms made. These films revealed a rather bizarre picture. The opaque solution filled countless vascular loops which were present in the foot. In the main however, there were four groups of dilated vessels, two toward the lateral borders and two in the region of the heads of the metatarsal bones. The individual vessels could not be identified. At the periphery of the vascular loops, the

FIG. 1.—Case 1: Photograph showing the large ulcer and scar on the plantar surface of the foot. Note the distortion of the foot by irregular, nodular swellings.

FIG. 2.—Case 1: Preliminary roentgenogram showing the phlebolith in the region of the cuboid bone. Note the thinning of the cortex on the inner surface of the fourth metatarsal bone and of the base of the fifth metatarsal bone.

radiopaque substance produced a peculiar feathery or "hair-brush" appearance. The outlines of the bony structures were almost completely obliterated by the injected vessels (Fig. 3).

The injection was followed by partial occlusion of the vessels, with reduction of the swelling of the foot. In view of the favorable result, the procedure was repeated three weeks later, using 2 cc. of a 5 per cent sodium morrhuate solution but selecting on this occasion the plexus beneath the external malleolus for injection. Three subsequent injections of sodium morrhuate were employed to occlude isolated groups of veins. Following the use of the sclerosing medium, there was a temporary copperish discoloration of the skin which quickly subsided. Within ten days, the pain had disappeared. In six weeks, the ulcer had healed and the patient was able to walk about and soon engaged in the usual normal activities of a boy of his age. Subsequent attempts to reinject the larger vessels were unsuccessful because they had been completely occluded. Figure 4 is a photograph of the foot taken three years after treatment. This patient was seen about six months ago, at which time a few small, patent vessels were still present between the first and fifth metatarsal bones but these were symptomless and too small to require further treatment.

Case 2.—Hosp. No. J-8127: T. G., male, age three, was seen July 21, 1937. The

mother stated that the child has had "red spots" and irregular painful swellings in the right forearm and hand since birth.

Physical Examination.—Flat, fluctuating masses were felt on the dorsal surface of the right forearm at the junction of its middle and distal one-third. These masses measured about one and three-quarter inches in diameter, were somewhat sensitive and apparently not attached to the bones. Many dilated veins were noted on the palmar surface of the hand. The skin was somewhat bluish in color and redundant as though frequently stretched. There were no evidences of acute inflammation. The Kahn and tuberculin tests were negative.

FIG. 3.—Case 1: Roentgenogram after injection of skiodan showing all the bony landmarks obscured by the radiopaque solution in the vascular loops. Feathery "hair-brush" appearance of vessels.

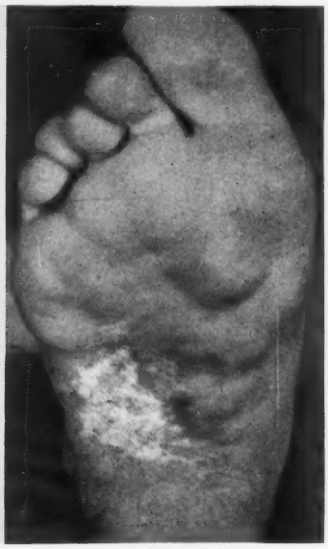

FIG. 4.—Case 1: Photograph three years after injection showing the scar replacement of the original ulcer and the restoration of the contours of the foot.

Preliminary roentgenologic examination showed the right ulna slightly increased in width. The medullary canal was ill-defined and in the middle one-third of the shaft was obliterated, whereas in the proximal one-third it appeared to be slightly expanded. The cortex was thinned out, somewhat irregular in contour, and, in scattered areas, split longitudinally. The periosteum was irregularly thickened. In the soft tissues of the forearm at about the level of the junction of its middle and distal one-third and somewhat posteriorly placed, there was a fusiform soft tissue swelling within which a phlebolith was visualized. The shafts of the third, fourth, and fifth metacarpal bones as well as the proximal phalanx of the fourth finger showed changes identical with those in the ulna. Numerous other bones of the skeleton were examined and found to be negative.

On November 7, 1935, large veins on the volar aspect of the forearm were distended by means of a tourniquet and 6 cc. of diodrast injected. Roentgenograms, taken immediately, showed numerous, fairly large clumps of vessels in the soft tissues of the forearm from its middle one-third to the elbow joint posteriorly. Identification of the individual loops was impossible. Several scattered phleboliths were noted (Fig. 5).

Examination of the forearm, one week later, showed the masses to be definitely harder and the veins less prominent. There were still, however, several dilated veins in the lower end of the forearm and these were injected with 2 cc. of sodium morrhuate.

Shortly thereafter 6 cc. of diodrast were again injected in order to map out the tumor. The roentgenogram revealed a somewhat elliptical group of vessels on the inner and posterior surfaces of the forearm extending from the level of the styloid process to the middle of the ulna. Some of the collateral vessels were outlined but the main stream of the dye detoured around, but did not fill, the preexisting tumor. It was apparent, therefore, that it had been completely sclerosed (Fig. 6).

Examination of the patient, three weeks later, showed that the tumor of the forearm had been completely obliterated, pain had disappeared, and the nevus was lighter in shade.

Case 3.—Hosp. No. 66079: A. B., colored, female, age three, was admitted August 14, 1937. The mother stated that since birth she had noted a smooth tumor of the left lower extremity which grew slightly as the child developed. Although there was no pain while at rest, the child complained at times after walking short distances. The mother stated that she herself has had a positive Wassermann for the past two years. Blood and spinal Wassermann examinations on the child done elsewhere, however, were reported negative.

FIG. 5.—Case 2: Roentgenogram after injection of diodrast showing innumerable dilated vascular loops. Note the soft tissue swelling in this area.

FIG. 6.—Case 2: Roentgenogram after injection of lower group of dilated vessels. Note that the original tumor has been obliterated, and the main stream of the dye detours around the preëxisting tumor.

Physical Examination.—The lower extremities were of equal length but the circumference of the left leg measured eight inches, whereas that of the right leg measured seven and one-half inches. On the anterior surface of the left leg, there was a hard, irregular swelling which seemed to be adherent to the skin. There was, likewise, a swelling on the internal and dorsal aspects of the foot but this swelling was softer than the mass in the leg and definitely movable. Lymph nodes could be palpated in the cervical, inguinal, axillary, and epitrochlear regions.

Roentgenologic examination disclosed an irregular soft tissue mass at the level of the middle one-third of the left leg anteriorly, which appeared to extend backward into the muscles of the calf. There was, likewise, a soft tissue swelling on the dorsum of the foot, which extended to its lateral borders. There was no disease in any of the bones of the left leg or foot.

Because the condition had existed since birth, the presence of the adenopathy, and since the mother was a known luetic, it was considered syphilitic in origin. Accordingly, 0.12 Gm. of neosalvarsan was administered intravenously and shortly thereafter, 0.5 cc. of bismuth subsalicylate was given twice weekly for several weeks. The Wassermann and Kahn tests, twice repeated, were pronounced negative, but despite this fact the antiluetic therapy was continued. About this time, the results of a previous biopsy of the mass, performed at another hospital, were communicated to us. The interpretation of that section was "chronic granulomatous tissue." The patient was discharged October 6, 1937.

On October 15, 1937, the child was readmitted. At this time, there was a fairly pronounced limp, and edema of the left lower extremity. The circumference of the left leg at this time was eight and one-half inches and of the right leg, seven inches. Antiluetic therapy was again instituted. Roentgenologic examination, at this time, disclosed a pyriform, circumscribed soft tissue mass on the posterior and internal aspect of the calf. There was no involvement of the underlying tibial shaft. Because of our previous experience, the suggestion was made that we might be dealing with a muscle angioma. After a period at the hospital, during which antiluetic treatment was continued, the patient was discharged unimproved.

On February 7, 1938, the patient was admitted for the third time. The mother stated that for a time since the previous discharge the child had felt quite well. The swelling of the left leg had practically disappeared and the child had been able to carry on the usual activities of a youngster of this age. About two weeks ago, however, the left leg and foot became swollen overnight. Although there was no definite discomfort at first, the pain during the last few days, however, had returned and become increasingly severe.

Physical Examination, at that time, revealed a generalized swelling of the left lower extremity from just above the knee joint to the toes. There was, in addition, local swelling behind and below the malleoli. There was a scar over the middle of the tibia on its anterior aspect. At the upper portion of the scar, there was a little thickening, and about two inches below the spine of the tibia, overlying the crest, there was a small hard mass measuring about one-half by three-eighths of an inch, attached to the skin and freely movable on the underlying tissues. There was a generalized swelling of the leg. Two discrete, slightly tender masses were noted behind the external malleolus. In both groins, there were rather discrete, shotty, lymphadenopathies. No epitrochlear nodes were felt but there was a slight axillary adenopathy. Again, antiluetic therapy was advised. In the absence of all therapeutic response, a biopsy was performed February 9, 1938. The surgical pathology showed: "Underlying the skin, was found a firm mass which was completely encapsulated and which could be bluntly dissected from the surrounding tissues. At the upper pole of the mass, a nerve was seen running into it. This mass was split and the nerve followed through its entire course into, through, and out of it. It was possible with extreme care to free the nerve completely from the mass. Within the tumor, were areas of old hemorrhage and cysts containing clear straw-colored fluid. Bleeding was easily controlled."

The report of the section removed at operation (Path. No. B-18593) was "diffuse angiomatosis of the leg." About a fortnight later 20 cc. of hippuran was injected into the mass of veins on the dorsum of the leg. The roentgenogram revealed a generalized, diffuse dilatation of the vessels of the calf as well as in the popliteal area. Small, circular densities suggested the presence of phleboliths (Fig. 7).

The patient was seen in October, 1938. There was an excellent result from the injection, most of the dilated veins had been obliterated but there was still present a few radicles in the foot which were to be further treated but the patient disappeared from observation.

Case 4.—Hosp. No. F-07085: H. B., male, age 17, was seen May 28, 1934. The patient stated that he had been struck on the inner and posterior surfaces of the left elbow joint, 14 years previously, and that four months later, he developed a soft tissue swelling in this area which had progressively enlarged.

Physical Examination revealed a lobulated, semielastic mass on the ulnar surface of the elbow joint and extending as far forward as the interosseous ridge of the humerus. This mass appeared to contain fluid and seemed to communicate with the elbow joint. Supination and pronation were slightly, if at all, limited. The ulnar nerve could be felt running through the tumor and it appeared to be displaced from its normal bed. Pressure

over the swelling caused a typical ulnar nerve response but there was no evidence of ulnar nerve paralysis. The Wassermann and Kahn tests, performed immediately after admission, were negative.

Roentgenologic examination revealed a fusiform, soft tissue mass on the ulnar surface of the forearm extending from the internal condyle of the humerus to the distal one-third of the ulna. Within this tumor, several phleboliths were demonstrated. There was some irregularity in the cortex of the ulna adjacent to the mass.

On July 9, 1934, the patient was operated upon and "a huge mass containing bloody fluid was encountered. As soon as dissection was started, a great deal of bleeding resulted. As the muscles were divided, a large cavity was found extending from the epicondyle down to the lower one-third of the forearm on its medial aspect. There were no veins or any other abnormal tissues in the cavity except two rounded masses, one having the color of a rice body and as large as a pea and, the second, black in color and about the size of a lentil."

FIG. 7.—Case 3: Roentgenogram after injection of hippuran showing diffuse dilatation of the vessels of the leg. Note the numerous phleboliths.

Pathologic Examination.—Section showed numerous bits of muscle and collagenous tissue. The larger lobulated body was a thrombus. Numerous thicker- and thin-walled blood vessels were seen.

Pathologic Diagnosis: "Intramuscular hemangioma."

Accordingly, shortly thereafter, 10 cc. of skiodan was injected into a prominent vein in the upper one-third of the forearm and roentgenograms made, which showed large clumps of dilated vascular loops on the inner aspect of the forearm in its proximal third. The upper limits of the mass reached the external condyle of the humerus and its outer edge was in intimate contact with the shaft of the ulna. Within the tumor, were numerous phleboliths which had been visualized previously (Fig. 8).

The patient was examined about one week later, and the tumor was found to be definitely smaller, and an additional 10 cc. of skiodan was injected. A subsequent attempt to reinject the vessels was only partially successful, as they were practically completely obliterated (Fig. 9). The patient was last seen about one year later and, at that time, the mass was considerably reduced in size, the vessels completely obliterated, and pain had completely disappeared.

CONCLUSIONS

By injections of radiopaque solutions, such as are commonly employed in intravenous urography, angiomata may be visualized and roentgenographically recorded. Although these chemicals possess sclerosing properties, they are best utilized for diagnostic purposes, and to determine the extent of

sclerosis following the injection of obliterating media. By the use of these chemicals, open operation may be avoided and satisfactory relief obtained.

FIG. 8.—Case 4: Roentgenogram after injection of skiodan illustrating localized dilatation of vessels. Radiopaque substance obscures the phleboliths.

FIG. 9.—Case 4: Roentgenogram one week after Figure 8. Second injection of skiodan fills only the superficial vessels. The large tumor is obliterated. Note the phleboliths.

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ACTIVE IMMUNIZATION AGAINST TETANUS

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RAMON and others[2-23] have proposed that vaccination with tetanus toxoid be employed as a routine public health measure in order to overcome the well known limitations of passive immunization and to provide a permanent immunity against tetanus.

Naturally, the first question that arises is how much antitoxin must be present in the blood to insure against the development of tetanus in the presence of a wound infected with *Cl. tetani*? No one knows. Animal experiments are inconclusive. Sneath, Kerslake, and Scruby[1] injected a lethal spore dose into a group of 55 guinea-pigs actively immunized by means of tetanus toxoid and found that 80 per cent of the animals were completely protected, 11 per cent were partially protected, and 9 per cent died of tetanus. From their studies it would appear that in the guinea-pig, the level of 0.01 unit of tetanus antitoxin per cc. of serum is a critical level in active immunization. Above that level, in 45 animals 13 per cent showed signs of tetanus, from which they recovered, while the remaining 87 per cent were completely protected.

The incidence of localized tetanus in 13 per cent of the immunized animals is, however, worthy of emphasis since in the human being, one must strive for complete protection in all cases.

In a similar type of experiment Cowles[2] encountered the same inconsistency in the antitoxin level required for protection as noted by Sneath and concluded that although it is probably impractical to define the minimum titer which will assuredly protect against tetanus, antitoxin values of 0.10 or 0.20 unit per cc. of serum can give a fairly certain protection in immunized guinea-pigs and mice at the time of infection. This author felt that though 0.10 unit is not sufficiently great to protect all animals against a maximum infection, it is probably much larger than is necessary to care for many infections resulting from wounds judged to be too slight for surgical attention, and probably large enough to care for the majority of injuries that receive surgical treatment.

Bergey and Etris[3, 4] have suggested that 0.01 unit may be satisfactory for protection. In a later publication[5] these workers maintain that 0.01 unit is "the least amount of antitoxin necessary for protection and is based on the finding in the serum of the person who showed least response to the antigenic effect of the toxoid one year after the second dose. This individual had 0.01 of a unit of tetanus antitoxin." This finding cannot, however, be accepted as indicating the protection level against infection.

We believe that, in the present state of our knowledge, active immunization must, to be of value, engender at least a titer equivalent to that produced

by the subcutaneous injection of 1,500 units of tetanus antitoxin. Serial titrations done by us[6] after such a prophylactic injection revealed the presence of 0.10 to 0.25 unit of antitoxin per cc. of blood serum (Chart 1). Hence we consider 0.10 unit as the minimum required for protection. It may be argued that this level is too high since less than 1,500 units may suffice for

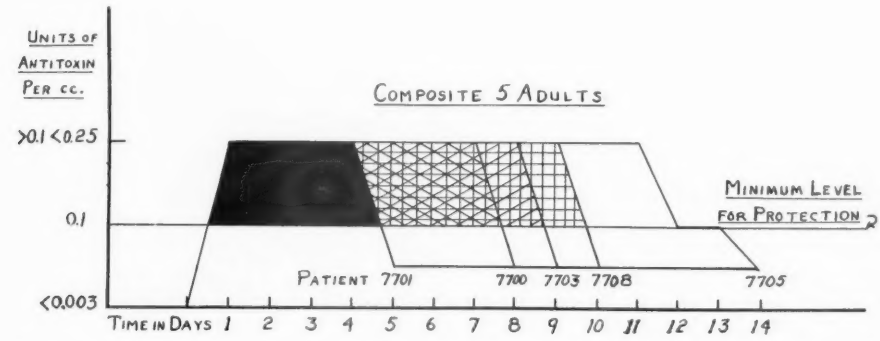

Chart 1.—Showing duration and extent of passive immunization following administration of 1,500 units of tetanus antitoxin.

passive immunization. Yet we feel that until direct and conclusive evidence exists on this point it is safer to err on the side of conservatism, and propose that no subject be considered immune unless he has at least 0.10 unit of antitoxin per cc. of serum following the injection of a primary course or "repeat" dose of tetanus toxoid.

Method of Immunization.—Two types of antigen are now in use. In France and Canada the plain tetanus toxoid is employed. The entire French Army as well as many thousands of civilians have been immunized with three doses of 1.0, 1.5 and 1.5 cc. of the plain toxoid given at intervals of three weeks. This schedule produces, according to Ramon, a high-grade immunity which lasts several years.[7, 8, 9]

In England, the Royal Air Force has been immunized with two 1.0 cc. doses of plain toxoid given about six weeks apart.[10] This schedule is based upon Boyd's[11] observations that two doses of plain toxoid given six weeks apart are as effective as three doses given at close intervals. In the United States, tetanus toxoid, alum-precipitated, has been used almost exclusively. Jones and Moss[12] working with both plain and alum-precipitated toxoids found that two injections of the alum preparation produced a greater and quicker immunity than three injections of the plain toxoid. Similar results were obtained by us.[13] We also found that the dose, the potency of the alum toxoid, and the interval between injections were important factors in determining the height and duration of the titer produced. Thus, when we[14] compared two series of patients that received different doses of the same lot of alum toxoid we found that at the end of 91 days after the second dose only 11.7 per cent of the group that received two 1.0 cc. doses dropped below 0.1 unit while in the 0.5 cc. group 42.8 per cent of the subjects showed less than 0.1 unit. At the end of 181 days 53.3 per cent of the 1.0 cc. group had less

than 0.1 unit while 75 per cent of the 0.5 cc. group dropped below this value. It is obviously not a question of volume alone but also of the antigenic potency of the volume injected. Thus 0.5 cc. of one lot of toxoid may be equivalent in potency to 1.0 cc. of another lot. The official standard for tetanus toxoid* is a minimum standard, and commercial preparations available on the market vary considerably in their potency.[15]

The length of time allowed to elapse between the two injections of alum toxoid is of definite importance. When the second injection of 1.0 cc. of alum toxoid was given by us one to four weeks after the first dose,[6] we failed to note any appreciable increase in titer. If given beyond this period a prompt and decided rise in titer occurred. McBryde,[16] Hall,[17] and Cowles[2] gave the two injections at intervals of 73 days, six weeks and 11 weeks, respectively. We prefer to inject them about three months apart because we feel that the longer interval favors the development of a higher antitoxic titer. Jones and Moss[23] have recently expressed a similar belief, although they had allowed a one month interval between the two injections.

Antitoxic Immunity.—The first injection of 1.0 cc. of alum toxoid does not result in any appreciable increase in the titer of most subjects. Only an occasional patient shows a rise to 0.1 unit. Apparently the first dose of toxoid prepares the antitoxin-producing cells in such a way that following injection of the second or subsequent doses there occurs a rather prompt release of antitoxin. This takes place even after five years have elapsed between the two injections. Age, sex, and color do not affect this mechanism. We have found that an acute infectious process such as lobar pneumonia interferes with the development of antitoxin while syphilis (latent) and active allergic states such as hay fever and bronchial asthma do not.

After the second injection, values of 0.10 to ten units per cc. of blood serum have been reported by us, and others.[2 to 6, and 12 to 23] To obtain equivalent titers would require the injection under the skin of many thousands of units of antitetanic serum (Table I). Naturally the rate of development of this protective titer is of utmost importance. After the second injection, five to 14 days may elapse before 0.1 unit of antitoxin appears in the blood. The maximum values are obtained at the end of one month. Thereafter, a loss in titer occurs which is most marked during the first three to six months. Some subjects show less than 0.10 unit at the end of three months but the great majority do not drop below this level until after six months. A few retain a good protective titer for more than two years. In the last seven years we have encountered only one refractory subject but he responded well to a third injection. Individual variations in antitoxin response are very prominent. Because of this and the absence of a simple test to determine the state of antitoxic immunity, it is necessary to raise the antitoxin titer of the blood to a protective level at the time of injury.

* A human dose (0.5 or 1.0 cc.) injected subcutaneously into guinea-pigs of 500 Gm. weight, shall, in a period of four to six weeks, engender at least two units of antitoxin per cc. of serum.

TABLE I

TETANUS TOXOID, ALUM-PRECIPITATED

Basic (Primary) Course: Two 1.0 Cc. Doses given 90 Days Apart

Number of Subjects Tested	Time After Second Dose	Titers in Units of Antitoxin Per Cc. of Blood Serum Number of Subjects							Percentage of Subjects with 0.10 Unit or More
		−0.10	0.10	+0.10 −0.25	0.25 to 0.50	0.50 to 1.0	1.0 to 3.0	3.0 to 10.0	
14	1 wk.	4	1	1	8*	—	—	—	71.4%
16	2 wks.	—	—	—	13†	—	2	1	100 %
153	1 mo.	—	3	19	14	29	71	17	100 %
60	3 mos.	5	6	—	24	18	6	1	91.6%
59	6 mos.	17	11	13	13	4	1	—	71.1%
50	9 mos.	21	18	4	4	2	1	—	58.0%
39	12 mos.	17	15	3	3	1	—	—	56.4%
30	20–22 mos.	21	3	2	3	1	—	—	30.0%

* Six subjects had +0.25 unit.
† Eleven subjects had +0.25 unit.
\+ More than.
− Less than.

Secondary Stimulation—"Repeat" Dose.—In 1927, Ramon called attention to the value of the injection *"de rappel."* Since then it has been definitely established that the injection of a third "repeat" dose of alum toxoid (secondary stimulus) will effectively raise the titer above the level of protection. Titers of 0.25 to more than ten units have been reported after such a "stimulating" dose.[2, 13, 18, 21, 23] Again, the rate of increase of the titer is of the utmost importance. To be effective the increase must be rapid, before the incubation period of tetanus expires. The latter is usually given as from six to 14 days and is directly proportional to the amount of toxin and the severity of the disease. We[21] have found that five to seven days elapse after the "repeat" injection before a titer of at least 0.1 unit appears in the blood (Table II). This should prove satisfactory since we are dealing here with an

TABLE II

TETANUS TOXOID, ALUM-PRECIPITATED

Antitoxin Response to a "Repeat" Third Dose (1.0 Cc.) given Nine to Twelve Months After Completion of Basic Course of Immunization

Number of Subjects Tested	Time After Third Dose	Titers in Units of Antitoxin Per Cc. of Blood Serum Number of Subjects							Percentage of Subjects with 0.1 Unit or More
		−0.10	0.10	+0.10 −0.25	0.25 to 0.50	0.50 to 1.0	1.0 to 3.0	3.0 to 15.0	
1	2 days	1							0 %
5	3 days	4	1						20 %*
14	4 days	12		1	1				14.2%
16	5 days	1	2	2	5	1	5		93.7%
7	6 days	1		1	2		3		85.7%*
24	7 days				2	2	11	9	100 %
31	1 mo.			1	2	3	13	12	100 %
27	3 mos.			1	6	6	12	2	100 %
28	6 mos.	3	2	3	7	8	5		89.2%
21	9 mos.	3	3	3	4	5	3		85.7%
19	12 mos.	3	2	3	7	4			84.2%
15	15–19 mos.	5		4	5	1			66.6%

* Percentage irregularity accounted for by small number of subjects tested.
\+ More than.
− Less than.

active immunity that is actually on the increase. It has also been reported by Jones and Moss,[23] and by us,[21] that after injection of the "repeat" dose there is a tendency for the titer to be retained over a longer period of time than after the basic course of immunization. This is well illustrated by a comparison of the titers in Tables I and II.

McBryde[16] and others[11, 41, 42, 43] have suggested that if the wound of an immunized subject became infected with tetanus spores, protection would be maintained by an outpouring of antitoxin in response to the first threat of invasion by toxin. If true, this would be of tremendous value because it would make any further "repeat" injections of toxoid unnecessary. No human observations exist on this point. Jones and Jamieson[24] found that a massive dose of tetanus spores did not markedly accelerate the production of antitoxin in guinea-pigs that had been previously immunized with alum toxoid. Some of the animals had as high as four units and yet they developed localized tetanus from which, however, they recovered. Boyd[11] interprets Jones's results differently. He argues that the titer in the test animals was so high that it is probable that the toxin produced by the germinated spores was immediately neutralized and failed to reach the reacting mechanism in a form capable of provoking antitoxin production. Wolters and Dehmel[25] have presented experimental evidence that actively immunized animals may survive spore infections with production of increased titers. In a very interesting study, Zuger, Greenwald, and Gerber[26] found that guinea-pigs immunized with a single injection of 1 Ml. of tetanus toxoid will react subsequently with an increased antitoxin titer when infected with a lethal dose of spores. The rise in titer will first be evident on the seventh day after infection in some of the guinea-pigs, especially in those that are without symptoms or if with symptoms, in those that will recover. This rise is small, a significant one not taking place until the eighth to tenth day, in contrast to the significant rise in titer that takes place on the fourth to fifth day when similarly prepared animals are given toxin instead of spores. They also found that when an additional dose of toxoid is injected simultaneously with the spores, a significant rise in titer is evident on the fifth day. The authors concluded that there is no evidence that the increase in titer induced by infection with spores can have sufficient protective effect, as hoped by some.[16, 42, 43]

From these studies it is clear that a "repeat" injection of toxoid should be given whenever an injury occurs.

Associated and Combined Immunization.—The French were the first to call attention to the possibility of simultaneous immunization against several diseases by the injection of mixed antigens. Ramon and Zoeller,[7, 27] and Sacquepee, Pilod, and Jude[28, 29] have reported on the use of an "associated" triple vaccine against typhoparatyphoid fever, diphtheria and tetanus. Immunization was accomplished by the injection of three doses of this triple vaccine followed by an injection "*de rappel*" for the purpose of reenforcing the diphtheria and tetanus antitoxin titers. In this country Jones and Moss[22, 23] have reported on the use of a combined diphtheria and tetanus toxoid, alum-

precipitated. They found that a good basic immunity was established by this mixed antigen and that its injection as a stimulating dose produced not only an immunity that was much greater than that obtained with the two primary injections but one that was prolonged over a much greater interval. They also found that the combined toxoid did not interfere with the specific immunity response to each disease.

In addition to this "associated" immunization against several distinct diseases, Ramon[30] has also proposed the use of the combined active and passive method of immunization for the prophylaxis and treatment of tetanus. He found that active antitetanic immunization could be realized by the simultaneous injection at the time of injury of both antitetanic serum and toxoid, followed by two doses of toxoid alone, at intervals of two or three weeks. Patients treated by serovaccination have the same antitoxic response to a subsequent "reenforcing" dose of toxoid injected several months or a year later, or later still, as patients who had been vaccinated with toxoid alone. These findings have been confirmed by Sacquepee and Jude.[31, 32, 33]

In the presence of tetanus, Ramon, *et al.*,[34] advise the administration of "150,000 I.U. of antitetanus serum and 2 cc. of tetanus toxoid given in different sites. Gradually progressive doses are then repeated at intervals of five or six days—2, 4 or 6 cc. of toxoid for instance. Later, 'reenforcing' doses of toxoid may be given, they are harmless and of real benefit. Ramon stated that experimental investigations and clinical tests made upon patients brought evidence that active immunization due to injections of toxoid follows without interruption of the passive immunization due to serotherapy." This observation is of crucial importance because of the possibility that the injected antitoxin serum (passive immunity) would neutralize the toxoid *in vivo* and thus interfere with the development of an active immunity. Complete agreement on this question does not exist as yet. Thus, Otten and Hennemann[35] have recently reported that active immunity induced in the guinea-pig by formol toxoid appears to be inhibited by the presence of passive immunity. They found that the third to sixth week constitutes the critical period because at this time passive immunity becomes exhausted while active immunity has not reached the required level. We are now investigating this problem.

Secondary Stimulation by the Intranasal Route.—Because tetanus toxoid must be injected repeatedly for stimulating purposes, we have investigated the possible use of other routes for the administration of the antigen. We[15, 36] have found that after a basic (primary) immunity has been established by the injection of two doses of alum toxoid given three months apart, we are able to raise the antitoxin level of the blood by the instillation in the nose of a specially prepared tetanus toxoid (Topagen*). The administration of two to three drops (about 0.1 cc.) of tetanus toxoid Topagen in each nostril on three successive days will raise the antitoxin titer to a protective level (0.1 unit or more) in seven to 14 days (Table III).

* Manufactured by the Mulford Biological Laboratories, Sharp & Dohme.

TABLE III

INTRANASAL STIMULATION WITH TETANUS TOXOID TOPAGEN

Three Daily Intranasal Instillations Given in Lieu of a Third "Repeat" Injection, Seven Months After Completion of the Basic Course of Immunization

Antitoxin Response 14 Days After the First Instillation

Number of Subjects Tested	Control* Titer	Titer in Units of Antitoxin Per Cc. of Blood Serum After Intranasal Stimulation Number of Subjects							
		0.10	+0.10 −0.25	+0.25 −0.50	+0.50 −1.0	+1.0 −3.0	+3.0 −5.0	+5.0 −10.0	+10.0 −15.0
90	−0.10	1	9	17	20	27	12	4	−
5	0.10	−	−	2	−	3	−	−	−
26	+0.10 −0.25	−	−	4	7	7	5	2	1
9	+0.25 −0.50	−	−	−	−	4	3	2	−

* Control bleeding obtained just before first instillation.
\+ More than.
− Less than.

The nasal treatments should be repeated every six to 12 months in advance of an injury. Experience to date, covering a large series of subjects that have been followed-up for more than a year, suggests that this combined method of active immunization by the subcutaneous and intranasal routes is a safe, simple, and effective means of producing and maintaining a solid immunity against tetanus. Its advantages are obvious.

Reactions.—The injections of tetanus toxoid, alum-precipitated, produce in many subjects a local reaction that varies in intensity. This local inflammatory response is more prone to occur if the toxoid is injected superficially under the skin, and is apt to be more intense after repeated injections of toxoid. It usually subsides in 24 hours. Occasionally, there is an associated aching and malaise. The most important reaction encountered is that due to sensitization. This may assume the form of anaphylactic shock, urticaria, or bronchial asthma. The French,[7, 8, 9] whose experience covers many hundreds of thousands of injections, have failed to report any untoward reaction. The British[10, 37] have encountered two cases of nonfatal anaphylactic shock following the second injection of plain tetanus toxoid. Both patients gave positive skin tests to Witte peptone which was present in the injected toxoid. In this country, Cooke[38] has called attention to the sensitizing properties of alum toxoid due to the presence of peptones and has reported several instances of allergic reactions such as asthma and hives following the second injection of alum toxoid. He recommended the use of a synthetic medium for the growth of *Cl. tetani* and the routine performance of skin tests prior to the toxoid injection. We[39] have reviewed the collective experience of several workers in this field and found only two cases of urticaria in over 1,700 immunizations with two or more doses of alum toxoid. Similarly, Hall,[41] in a review of his large experience at the U. S. Naval Academy, encountered four instances of urticaria and one of frank anaphylactic shock among 1,800 subjects that had received a second dose of "inadequately washed," alum-precipitated, tetanus toxoid. No reaction occurred following the injection of a

second dose of a well prepared toxoid in 1,293 additional subjects. Hall concluded that an alum-precipitated toxoid, thoroughly washed, is a safe immunizing agent and should not produce reactions of sensitization. The paucity of reports of clinical sensitization is in marked contrast to the high frequency of positive skin tests to the various components of the toxoid (especially to the peptone) obtained by us.[39] Moreover this lack of correlation between the skin and the clinical evidences of sensitization is further illustrated by our ability to administer to four patients a full dose of tetanus toxoid, alum-precipitated, in the presence of marked positive skin tests without any untoward reaction. Actually, two of the subjects were asthmatic children. Hence, we feel that skin tests with tetanus toxoid are not a reliable guide for the detection of clinical sensitivity which may occasionally develop following injection of the toxoid. As in any other immunizing procedure epinephrine HCl should be kept on hand for the control of any reaction. In this respect, it is perhaps worth while to recall the fact that in 1927 Ramon and Zoeller[40] reported on the successful use of the intranasal route for immunization against diphtheria in subjects that were extremely sensitive to diphtheria toxoid and could not tolerate its injection.

CONCLUSIONS

Active immunization against tetanus is both practical and safe. A basic (primary) immunity can be established by the injection of two doses (0.5–1.0 cc.) of alum-precipitated or plain toxoid given about three months apart. Thereafter, a "repeat" injection of toxoid (1.0 cc.) should be given whenever an injury occurs. This will serve to raise the antitoxin level of the blood of the immunized subject to a protective level. In lieu of these "repeat" injections, intranasal instillations of tetanus toxoid Topagen (0.1 cc. in each nostril, on three successive days) can be given with advantage. These instillations should be repeated periodically every six to 12 months. They will then produce a solid immunity against tetanus, in advance of an injury. It also appears that immunization against tetanus, diphtheria, and typhoid fever can be accomplished simultaneously by the injection of a mixed antigen.

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THE INFLUENCE OF TEMPERATURE ON WOUNDS

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THE USE of local applications of heat or cold for the treatment of disease is as old as recorded medicine. Hippocrates recommends the application of heat by fomentation for the relief of pain in "acute disease" but warns that if the pain is not relieved, one ought not to foment for a length of time because this dries the lungs and promotes suppuration. Within comparatively recent times, hot poultices of a great variety of composition constituted a very large part of the therapeutic methods employed, but the faith in the efficacy of the substance or drug composing the poultice largely gave way to the opinion that any beneficial effect of the poultice was solely due to the fact that it was a means of local application of heat.

Although some practitioners of medicine still believe that hot and cold applications each have their peculiar indications, most physicians probably agree with John Hunter that neither hot nor cold applications have any considerable influence on the development of any pathologic process. There is ample evidence for the truth of this statement in the frequency with which practitioners of medicine state that the choice of hot or cold applications, as well as the method employed, is dependent solely on the comfort derived by the patient.

In a previous publication[1] the authors have reported an experimental study in which it was shown that temperature was an important factor in determining the length of survival of living tissues completely deprived of circulation. The purpose of this paper is to report the results of an experimental study of the influence of temperature on the reaction of living tissues to injury.

The first experiments consisted in performing, with careful aseptic precautions, abdominal incisions in dogs, in some of which the wound was contaminated by a standard dose of a broth culture of *Staphylococcus aureus*. Contaminated wounds and presumably uncontaminated wounds were permitted to heal at body temperature, and a number of both types of wounds were subjected to both hot and cold applications during the period of healing. These experiments showed a very marked influence of temperature on both the gross and microscopic characteristics of the healing wounds. All of these experiments, however, were discarded because of the lack of complete control over such factors as unknown bacterial contamination, differences in degree of hemostasis, differences in interference with blood supply to tissues, and differences in amount of trauma inflicted, which would not only vary in different wounds but in the different parts of the same wound. The experimental method employed in the experiments forming the basis of this paper not only excluded the uncontrollable factors necessarily associated with an

abdominal incision, but produced a wound sufficiently small for the entire diameter of the wound to be included in a single microscopic section.

Dogs were used as the experimental animal. Since it was necessary to restrain the animal throughout the entire course of the experiment, anesthesia was constantly maintained by repeated subcutaneous injections of morphine sulphate. After the removal of the hair from the entire back, the skin was cleaned with green soap, iodine and alcohol. Three pairs of symmetrical points were chosen so that two of these points could be subjected to the application of heat and two to the application of cold; while the third pair was not influenced by either hot or cold applications. At three of the points chosen, 0.1 cc. of oil of turpentine was injected intracutaneously with a No. 27-gauge hypodermic needle. At the other three sites chosen, 0.1 cc. of a 24-hour broth culture of *Staphylococcus aureus* was similarly injected. The *Staphylococcus aureus* used was obtained from a culture which had been propagated in the laboratory for a period of years, during which time it had maintained a constant virulence.

To each side of the animal's back was fitted a thin rubber bag which covered two areas of injection: one of turpentine and one of *Staphylococcus aureus*. The remaining two sites of injection, one of turpentine and one of *Staphylococcus aureus*, were placed sufficiently far away so as not to be influenced by any alterations in temperature from the rubber bags. An appropriate system of tubes and electric pumps maintained a constant circulation of cold water through one bag and hot water through the other. Frequent measurements of the temperature at the point of contact between the rubber bag and the skin showed that on one side the temperature remained at approximately 10° C., while on the opposite side the temperature remained at 40° C. All of these experimental lesions were as superficial as it seemed possible to produce a lesion appropriate for this study. Since all of the tissues studied

EXPLANATION OF PLATES

PLATE I, FIG. 1.—Actual size color photograph of a lesion 48 hours after the intradermal injection of 0.1 cc. turpentine. The lesion was developed without the application of either heat or cold. A central necrotic area is well-defined, and there is some evidence of beginning disintegration of the necrotic skin. A surrounding zone of inflammatory reaction is clearly shown.

FIG. 2.—The same lesion shown in Figure 1, but 24 hours later, at which time there is relatively little change in the appearance of the surrounding zone of inflammatory reaction, but there is further progress in the disintegration of the necrotic center.

FIG. 3.—Actual size color photograph of a lesion 48 hours after the intradermal injection of 0.1 cc. turpentine. Immediately after the injection, the lesion was kept continuously at a temperature of 40° C. The central necrotic area shows marked evidences of disintegration, and the area of surrounding inflammatory reaction is larger than the field included in the photograph. This surrounding area was much more edematous than in the lesion permitted to develop at body temperature.

FIG. 4.—The same lesion shown in Figure 3, but 24 hours after discontinuing the application of heat. There is some diminution in the apparent intensity of the surrounding inflammatory reaction. There is further liquefaction of the central necrotic area.

FIG. 5.—Actual size color photograph of a lesion 48 hours after the intradermal injection of 0.1 cc. turpentine. Immediately after the injection the lesion was kept continuously at a temperature of 10° C. The central necrotic area is not perceptibly changed in appearance from that immediately after the intradermal injection of turpentine. This area is surrounded by a narrow zone of increased redness which did not appear until more than 24 hours after the injection. There was no visible swelling nor edema. From palpation alone the lesion could not be differentiated from the normal skin.

FIG. 6.—The same lesion shown in Figure 5, but 24 hours after discontinuing the application of cold. The central area of necrosis has become clearly differentiated and the surrounding skin shows well developed acute inflammatory reaction. This lesion, which is actually 96 hours old, appears approximately the same as one 24 hours old, not subjected to cold or hot applications.

A comparison of Figures 5 and 6 shows not only the marked inhibiting effect of cold on the development of the reaction of living tissues to injury and on the postmortem changes which take place in necrotic tissue, but Figure 5 clearly shows the impossibility of determining the extent or even the presence of severe damage to living tissue before the development of any neighborhood response in living tissue or the appearance of postmortem changes in dead tissue.

PLATE I

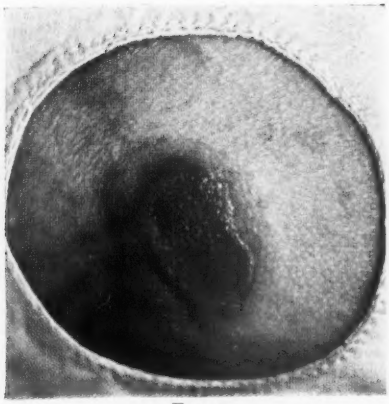

FIG. 1.

FIG. 2.

FIG. 3.

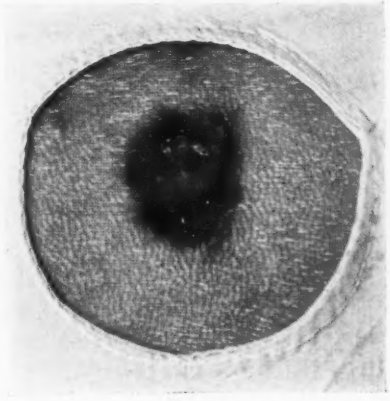

FIG. 4.

FIG. 5.

FIG. 6.

PLATE II

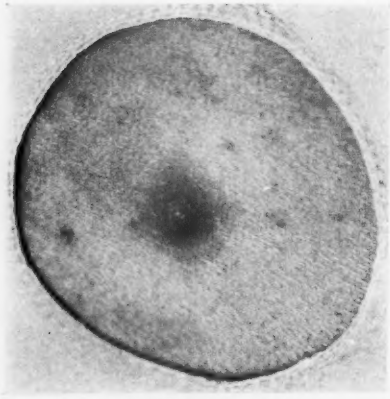

FIG. 1.

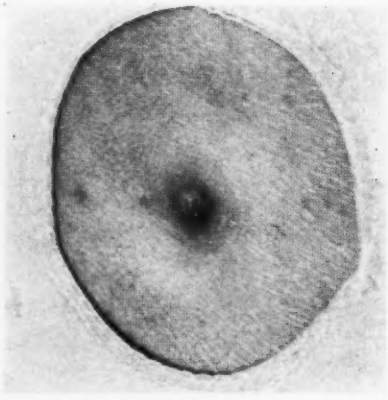

FIG. 2.

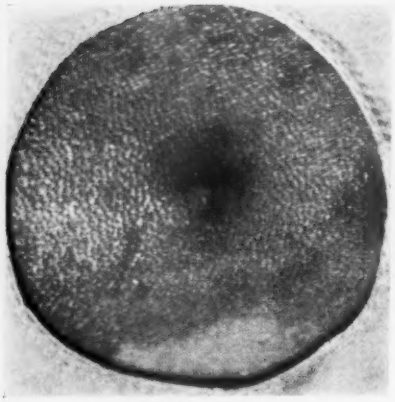

FIG. 3.

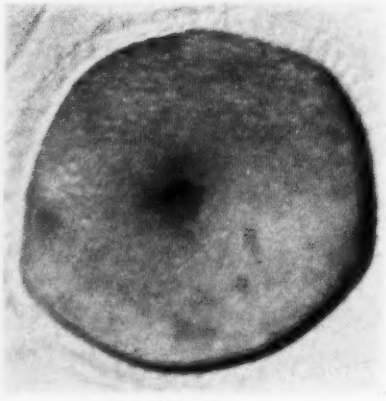

FIG. 4.

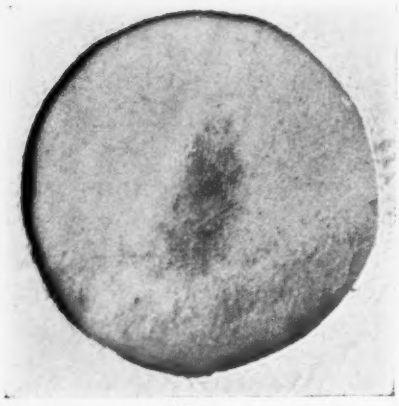

FIG. 5.

FIG. 6.

were within a distance of 0.5 cm. from a surface which was maintained at a constant temperature by hot and cold applications, it appeared that the depth of change of temperature in the tissues need not be considered as an important influential factor. Evidence that hot or cold applications do not exert an influence to any great depth will be subsequently presented.

Since a previous experimental study[2] had demonstrated that constant pressure exerts marked influence on living tissues, the size and shape of the bag were arranged so that a minimum pressure would be exerted upon the skin, and each bag was connected with a manometer in order that the pressure exerted upon the skin was equal on each side.

(1) Results of Experiments in which Aseptic Necrosis was Produced.—In the lesions produced by intradermal injection of oil of turpentine, the area of necrosis in the skin was clearly visible a few minutes after injection, as an opaque yellowish spot approximately one centimeter in diameter. If the temperature of the necrotic area and the surrounding skin is maintained at 40° C., there is at the end of three hours definite induration of the lesion with some swelling of the surrounding skin. At the end of 24 hours there is a marked increase in the amount of swelling of the surrounding skin and a zone of redness occurs around the opaque yellow center. The intensity of the inflammatory reaction at this stage is shown in Plate III, Figure 1. At the end of 48 hours the acute inflammatory process has fully developed in the skin surrounding the lesion, and the necrotic center is beginning to show definite evidence of disintegration by autolysis (Plate I, Fig. 3).

If immediately after the intradermal injection of turpentine, the lesion produced is continuously maintained at a temperature of 10° C., there is at the end of 24 hours no further gross change in the lesion nor in the surrounding

PLATE II, FIG. 1.—Actual size color photograph of a lesion 48 hours after the intradermal injection of 0.1 cc. of a 24-hour broth culture of *Staphylococcus aureus*. The lesion was developed without the application of either heat or cold. There is an area of necrosis and suppuration with a relatively large area in which there are all the signs of acute inflammatory reaction, most intense nearest the site of injection. The extent and amount of the swelling and edema were more than is evident from the photograph.

FIG. 2.—The same lesion as shown in Figure 1, but 24 hours later, in which there is a diminution in the intensity of the inflammatory process in the skin not immediately adjacent to the lesion. There has been further liquefaction of the central necrotic area.

FIG. 3.—Actual size color photograph of a lesion 48 hours after the intradermal injection of 0.1 cc. of a 24-hour broth culture of *Staphylococcus aureus*. Immediately after the injection the lesion was kept continuously at a temperature of 40° C. There is a well-defined central necrotic area which shows definite evidence of softening and suppuration. The surrounding skin shows slightly more swelling and edema than about a lesion permitted to develop at body temperature. The intensity of the redness (partly due to the effect of heat on normal skin) is much greater than about the lesion developed at body temperature.

FIG. 4.—The same lesion as shown in Figure 3, but 24 hours after discontinuing the application of heat. Unfortunately, the camera was not accurately focused when the photograph was made, but it can be seen that there is diminution in the intensity of the inflammatory reaction on the skin not immediately adjacent to the site of injection. The central necrotic area has undergone further liquefaction until it has become separated from the surrounding living tissues.

FIG. 5.—Actual size color photograph of a lesion 48 hours after the intradermal injection of 0.1 cc. of a 24-hour broth culture of *Staphylococcus aureus*. Immediately after the injection the lesion was kept continuously at a temperature of 10° C. The only change which is shown in the skin at the site of the injection is a small area of bluish discoloration. (Note: The small red spots in the surrounding skin shown in the photograph are produced by the shaving of the animal's hair previous to injection). From palpation alone it was impossible to locate the site of the injection. There was no visible redness or edema. This shows that low temperature will inhibit the development of those conditions which usually make it possible to determine the extent and magnitude of damage to tissues.

FIG. 6.—The same lesion as shown in Figure 5, but 24 hours after discontinuing the application of cold, three hours after which the manifestations of an acute inflammatory process appeared in the skin surrounding the site of injection. Twenty-four hours after removal of the cold applications, the central necrotic area is clearly differentiated. It is interesting, and perhaps important, that this necrotic area was in most instances considerably larger than those in similar lesions developing at body temperature.

skin, and a microscopic section shows no evidence of edema nor of leukocyte infiltration (Plate III, Fig. 2). At the end of 48 hours there is still no induration nor visible swelling. There is at this time only a narrow red zone surrounding the area of necrosis (Plate I, Fig. 5).

If the temperature of the area of necrosis produced by intradermal injection of turpentine is not altered by external application of either heat or cold, the intensity of the inflammatory process is distinctly less during any period short of 48 hours than about a lesion in the same period but which has been maintained at 40° C. (Plate I, Fig. 1). The difference between the lesion maintained at 37° C., and the one at 40° C. is less than that between the lesion at body temperature and one maintained at 10° C., and the differences are such as to suggest that if there were some method of measurement of rate of development of an acute inflammatory process, it would be proportionate arithmetically rather than geometrically to temperature in the range of 0° to 40° C.

(*II*) *Experiments in Which the Staphylococcus Aureus Was Injected Intradermally.*—The lesions produced by intradermal injection of the standardized strain of *Staphylococcus aureus* which were not subjected to the influence of hot or cold applications were remarkably constant in size, shape, extent of necrosis and rate of development. The lesion 48 hours after injection is shown in Plate II, Figure 1.

If the site of the intradermal injection of *Staphylococcus aureus* is maintained at 40° C., the physical changes of the inflammatory process develop more rapidly and are of greater magnitude and intensity. At 24 hours there is marked swelling, redness and induration about the lesion, and microscopic examination shows the characteristic picture of an acute suppurative inflammation (Plate III, Fig. 3). At 48 hours there is a central area of necrosis, softening, ulceration and a purulent discharge (Plate II, Fig. 3).

If the site of inoculation of *Staphylococcus aureus* is maintained at 10° C., there is at 24 hours a small area of slight discoloration (ecchymosis) about the puncture, and no visible change in the surrounding skin. Microscopic examination shows only an occasional extravascular leukocyte near the tract of the needle (Plate III, Fig. 2). It is interesting that there is more evidence of inflammation in the deep subcutaneous tissues in which there has been less reduction of the temperature. At 48 hours the discoloration of the skin immediately adjacent to the puncture is increased in intensity and slightly in extent and microscopic examination shows an increase in the number of extravascular leukocytes, but there is no evidence of edema and no evidence of necrosis. The gross characteristics of this lesion at 48 hours are shown in Plate II, Figure 5.

(*III*) *Changes in Experimental Lesions after Cessation of Hot and Cold Applications.*—It is important to call attention to the fact that any observation of a condition existing in a wound is only significant when it is related to past or future developments. A recent wound is in reality a combination and a mixture of many influential factors. The magnitude or even the presence in

PLATE III

FIG. 1. FIG. 2.

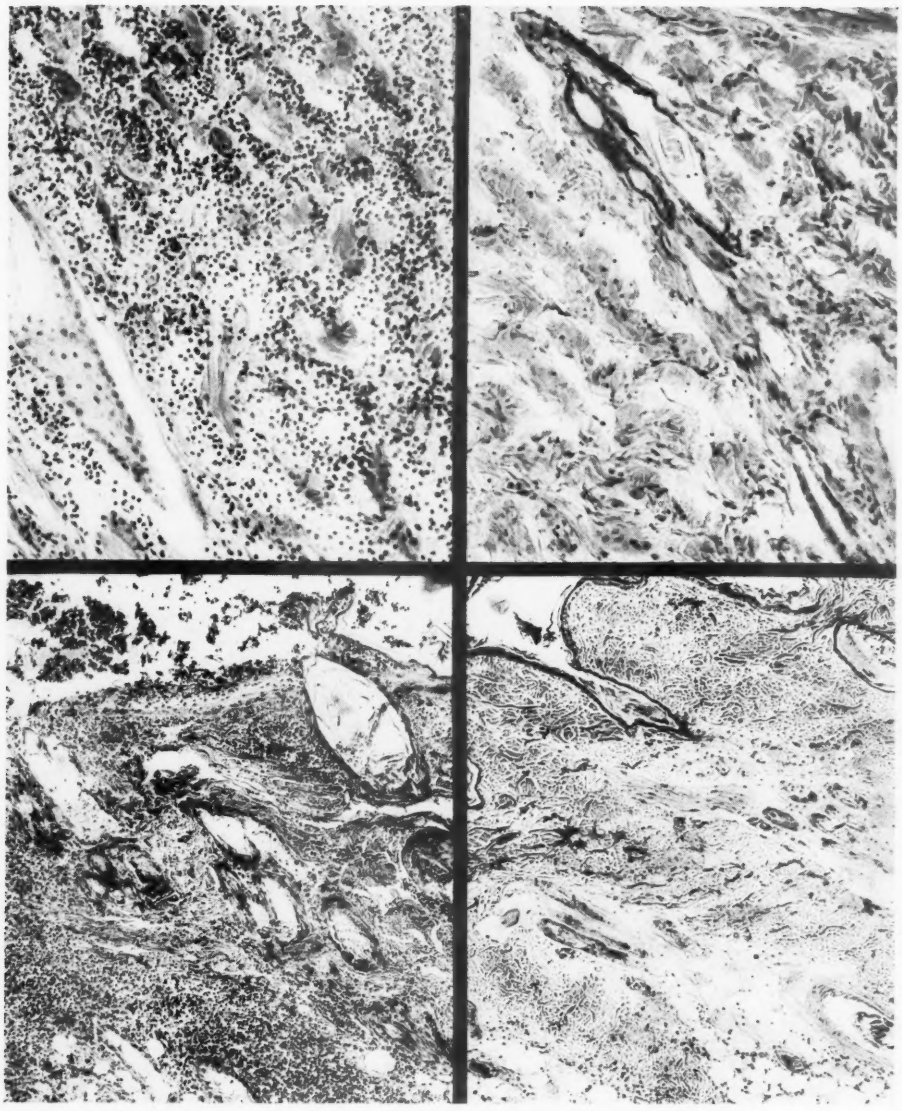

FIG. 3. FIG. 4.

FIG. 1.—Photomicrograph of a lesion 24 hours after the intradermal injection of 0.1 cc. turpentine. Immediately after the injection the lesion was kept continuously at a temperature of 40° C. The existence of a marked, acute inflammatory reaction is shown by the presence of edema and a large number of extravascular polymorphonuclear leukocytes.

FIG. 2.—Photomicrograph of a lesion 24 hours after the intradermal injection of 0.1 cc. turpentine. Immediately after the injection the lesion was kept continuously at a temperature of 10° C. Microscopic section shows no evidence of inflammation or necrosis.

FIG. 3.—Photomicrograph of a lesion 24 hours after the intradermal injection of 0.1 cc. of a 24-hour broth culture of *Staphylococcus aureus*. Immediately after the injection the lesion was kept at a temperature of 40° C. The section shows the characteristic microscopic picture of a severe acute inflammatory reaction. At the top of the illustration ulceration and the presence of purulent exudate are clearly visible.

FIG. 4.—Photomicrograph of a lesion 24 hours after the intradermal injection of 0.1 cc. of a 24-hour broth culture of *Staphylococcus aureus*. Immediately after the injection the lesion was kept continuously at a temperature of 10° C. The section shows no evidence of necrosis nor inflammatory reaction in the tissue nearest the surface to which cold was applied. The entire thickness of the skin appears quite normal. At the bottom of the illustration there is a definite infiltration of the subcutaneous fat by polymorphonuclear leukocytes. This figure clearly illustrates the marked influence which cold exerts upon the development of a tissue response to bacterial invasion. It also shows very clearly the relatively small depth of the influence exerted by the application of cold to the surface of a living healthy animal with a normal circulation.

large amount or the total absence of two of the most important of these influential factors, namely, injury to tissues and contamination with pathogenic organisms, can be determined only by future developments. From the examination of a microscopic section one could not testify as to whether the bloc of tissue from which the section was cut came from a living or dead body, nor whether it was killed before or after separation from the body. Likewise, a bloc of necrotic tissue in a living animal is subject to the same postmortem changes as would occur anywhere else with the same environmental conditions of temperature, moisture and bacterial contamination.

Experimental lesions produced by intradermal injections of *Staphylococcus aureus* and turpentine and subjected to both hot and cold applications were observed for varying periods after cessation of the hot or cold applications. The changes occurring in and about the experimental lesions during a period of 24 hours after discontinuing the applications of heat or cold were considered as the most reliable evidence for interpreting conditions existent at the time of removal of hot or cold applications. This period is long enough at a temperature of 37° C. for necrotic tissues to show obvious postmortem changes and for living tissues at body temperature to develop unmistakable signs of a response to injury. Some of the changes occurring during this period are evident from a comparison of the photographs reproduced in Plates I and II.

Plate I, Figure 5 is a photograph of the lesion produced by intradermal injection of 0.1 cc. turpentine to which cold has been applied for 48 hours. During this period there has been no demonstrable change in the central area and only very slight change in the surrounding skin, which is in sharp contrast to the marked changes which have occurred in and about the same lesion maintained at body temperature and shown in Plate I, Figure 1. Without any knowledge of subsequent developments, but with the information which could be obtained from the use of all available methods of examination of these experimental lesions as they exist at the end of 48 hours after their development at different temperatures, it would be difficult to avoid the conclusion that cold applications are an effective method of preventing undesirable consequences of intradermal injections of turpentine. Subsequent changes after removal of cold show that this conclusion is incorrect.

If cold applications to the experimental lesion produced by turpentine, and shown in Plate I, Figure 5, are discontinued at the end of 48 hours, the characteristic signs of an inflammatory reaction in the surrounding skin begin to appear in two or three hours. The central area becomes more discolored and definite signs of postmortem decomposition develop, and 24 hours after discontinuance of the cold application the lesion, which is now 96 hours old, is approximately the same as a similarly produced lesion developing at body temperature for 24 hours. Since lowering of the temperature of the skin after the injection of turpentine could hardly influence the time at which necrosis took place or the amount of tissue which was killed, the influence must have been one of inhibition of postmortem change in the necrotic tissue and of the inflammatory process in the adjacent living structures. Whether the reaction

in the adjacent structures is absent because of the inhibition of the tissue's normal response to a chemical poison (turpentine) or because of the inhibition of the production of toxin by autolysis of the necrotic tissue, is not known. This should be determined by a comparative study of the influence of cold applications in a similar manner to an area of necrosis produced by some method in which a necrotizing agent would not remain in the tissues, *e.g.*, coagulation by heat or freezing.

If experimental lesions produced by *Staphylococcus aureus* and maintained at temperatures above or below body temperature for 48 hours are observed for an additional period of 24 hours after removal of hot or cold applications, the changes which occur are illustrated in Plate II. The discontinuance of hot applications is followed by a diminution in the intensity of the redness of the surrounding tissues, but otherwise there are no more changes taking place than there are in a lesion subjected to neither hot nor cold applications. The lesion which has been subjected to cold applications for 48 hours, and which at this time is a small area in which there is only ecchymosis with no evidence of reaction in the adjacent tissue, begins in two to three hours after the removal of the cold application to be transformed into a lesion with a sharply differentiated central area of distintegrating dead tissue, surrounded by tissues showing the characteristics of acute inflammation. At the end of 24 hours the lesion does not differ in gross appearance from one developing at body temperature, except that it usually shows a slightly larger necrotic center.

Although these experiments demonstrate conclusively that temperature exerts a marked influence on the development of the inflammatory process and on the postmortem changes in necrotic tissue, no experiments were performed for the purpose of study of any influence temperature might exert on an inflammatory reaction which had already developed. The experimental lesions were the most superficial which could be produced and were, therefore, in structures whose temperature could be most influenced by external applications. The appearance of some reactive changes in the subcutaneous tissues indicated the relatively small depth of temperature alteration by the external applications. The impossibility of cooling the deeper structures, which are constantly being perfused by warm blood, is obvious. Furthermore, it is quite possible that cooling of the superficial tissues might operate to stimulate a more rapid development of reaction in the deeper structures in which there might be, because of a more abundant circulation, actually an increase in temperature.

Although the experiments in which the experimental lesion was produced by inoculation with staphylococcus were markedly influenced by changes in temperature, the mechanism of this influence was not determined. Whether the stimulus for the reaction was less because of inhibition of bacterial growth or diffusions of toxins, or whether there was an inhibition of reaction of the tissue, is not known. It is interesting that the area of necrosis which subsequently appeared after cold application was larger than if the lesion developed at body temperature.

It is also worth while to point out a possible bearing these experiments may have on the pathogenesis and treatment of surgical shock. Reduction of the temperature of the tissues certainly exercises a marked effect on the exudation of fluids into tissues and on the disintegration of devitalized tissues, so that no matter which of the two most generally accepted theories of shock is accepted, it would appear that the results obtained in these experiments do not support the generally accepted use of the application of external heat for the prevention or treatment of surgical shock. In surgical shock the temperature of the cold, bloodless extremities would be more influenced, *en masse,* than extremities with an abundant circulation.

These experiments at least suggest that there is reasonable doubt of the wisdom of inhibiting an inflammatory reaction by cold application or of the universal application of heat to the extremities of a patient in surgical shock. After all, these conditions are natural responses, and efforts to reverse normal physiologic processes bring to mind the now universally discarded fever reducing drugs of the past.

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[2] *Idem:* Arch. Surg., **40,** 696, 1940.

REGENERATION OF EPIPHYSEAL CARTILAGE*

AN EXPERIMENTAL STUDY

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THESE EXPERIMENTS were undertaken to determine the extent to which an epiphysis or epiphyseal growth cartilage may regenerate when either one or both has been partially or completely destroyed. That longitudinal growth of the shaft of bones which are preformed in cartilage occurs only from the anatomically intact epiphyseal cartilage plate has been accepted as a fact.

Selye[1] conducted experiments, the results of which he interpreted as reflecting some doubt on the complete accuracy of this theory. He performed midthigh amputations on rats 12 to 15 days old and at necropsy, 19 to 25 days later, found a layer of cartilage which closed the amputation end of the bone, and assumed this to be a growth cartilage. He did not state that it might have been cartilage of the callus repairing the cut end of the bony stump. Selye concluded, without demonstrating evidence adequate to support his theories, that "the growth of very young bones is largely independent both of the pituitary growth hormone and of the derivatives of the epiphyseal cartilage anlage." We also have attempted to either confirm or refute this hypothesis.

Methods and Materials.—Two distinct sets of experiments were performed, one on white rats and the other on rabbits. Sixty-one animals, 15 days old, were used in the rat experiments. The distal end of the left femur was exposed under ether anesthesia by reflecting the patella tendon, without stripping periosteum from the diaphysis. Table I shows the procedures that were then carried out:

TABLE I

Group		Number of Rats
A	Midfemoral amputation	25
B	Subtotal resection of lateral half of distal femoral epiphysis leaving the cartilage plate	13
C	Subtotal resection of distal femoral epiphysis leaving the cartilage plate	13
D	Resection of medial half of distal femoral epiphyseal cartilage plate	5
E	Complete resection of distal femoral epiphyseal cartilage plate	5
	Total	61

From Group A, one rat was sacrificed every second day from the seventh to the thirty-fifth postoperative day and the remaining ten rats at nine

* This study was aided by a grant from the Douglas Smith Foundation for Medical Research.

weeks. One rat in each of Groups B, C, D, and E was sacrificed at four weeks and the remaining rats at the end of nine weeks.

Results.—Group A—Midfemoral Amputation: The healing process was concerned primarily with the repair of the defect at the end of the bone, and was not influenced by the angle of the resection as related to the long axis of the femur. After seven days, a fibrous cap containing areas of fibrocartilage cells closed the amputation end of the shaft. After 15 days this fibrous cap had increased in thickness, and was microscopically similar to the callus of a healing fracture, containing fibrous tissue, osteoid tissue, cartilage, and

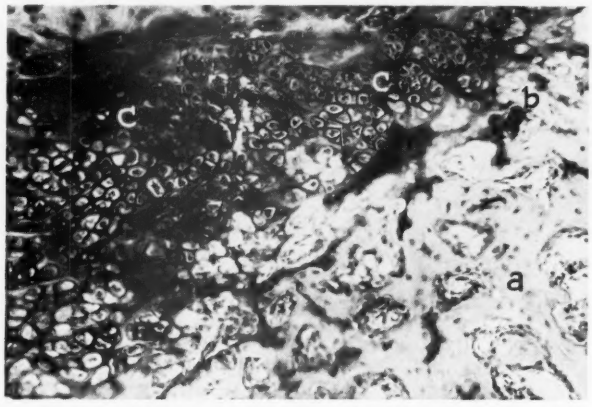

FIG. 1.—Photomicrograph of an amputation stump, 30 days after operation, showing a callus typical of a healing fracture of any young bone which is preformed in cartilage. The elements from the surface inward are (c) cartilage, (b) ossifying zone, (a) bone. (×240)

areas of calcification and ossification. The predominance of proliferating cartilage cells in the callus across the end of the shaft of some of the later specimen was striking (Fig. 1). We may reasonably assume that what Selye regarded as a regenerated longitudinal growth disk was this cartilage of the callus of repair. No length growth occurred from this tissue in the rats of our experiments. The complete microscopic analysis could leave no doubt that this cartilage was structurally and genetically identical with that which is commonly found in the callus of healing fractures in extremely young animals, or repair of defects of bones which are preformed in cartilage. Organization of the callus into mature bone was complete in four rats examined from the twenty-ninth to the thirty-fifth day. After a period of nine weeks, there was bony repair of all of the stumps, some of which were rounded and some conical.

Groups B and C—Subtotal Resection of Epiphyses: In these experiments, the lower femoral epiphysis was exposed anteriorly after lateral reflection of the tibiopatella tendon. In Group B, the lateral half of the epiphysis was cut straight across distal to the wavy epiphyseal line leaving behind a small amount of bone that was greatest along the outer aspect. In Group C, the epiphysis was cut completely across, leaving small amounts

of bone at the edges and in the intermediary notch. Resected portions of the epiphysis, including the articular cartilage, were not restored except for a small amount of proliferation of the bone that was left behind with the formation of a bony cortex. The defects were repaired, in part, by dense

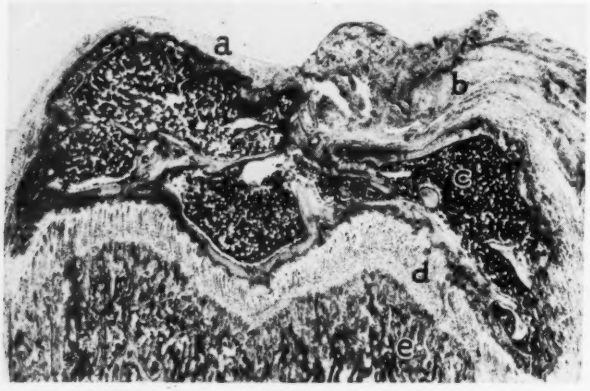

FIG. 2.—Photomicrograph of the distal end of a rat femur nine weeks following subtotal hemiexcision of the epiphysis. It shows fibrous tissue repair (b), some proliferation of bone of the ossification center (c), but no regeneration of the hyaline articular cartilage locally or by overgrowth from the unresected half of the epiphysis (a). The epiphyseal plate (d) is intact with normal longitudinal growth of the metaphysis (e).

fibrous tissue. In most cases of hemiresection there was overgrowth by this fibrous tissue with partial absorption of the articular cartilage of the remaining condyle. The joint space was obliterated by fibrous adhesions. Longitudinal growth of the diaphysis continued, providing the epiphyseal plate was not disturbed at operation (Figs. 2 and 3).

Group D—Hemiresection of the Epiphyseal Cartilage Plate: When the medial portion of the cartilage plate was excised, a bony bridge formed between epiphysis and diaphysis and growth on this side was arrested while longitudinal growth continued on the lateral side for a time. This resulted in an increasing deformity, characterized by tilting of the condyles of the femur, until the plane of the articular surfaces formed an acute angle with the long axis of the shaft, creating limb shortening and a marked varus deformity of the knee (Fig. 4 E).

Group E—Resection of the entire epiphyseal plate including thin sections of bony metaphysis and epiphysis produced immediate arrestment of longitudinal growth from this end of the femur. In four experiments there was bony union of the epiphysis and shaft, while in one nine-weeks experiment the epiphysis was ununited and markedly displaced on the shaft (Fig. 4 D). The four femurs from which the junction cartilage was removed, were only about two-thirds as long as the normal controls at the end of nine weeks.

A second group of experiments (Table II) was performed upon 20 rabbits, three days old. They were sacrificed in from six weeks to seven months after operation.

TABLE II

Group		Number of Rabbits (3 days old)
A	Cartilaginous head of the right femur was excised down to the epiphyseal plate	4
B	The entire head and part of the neck of the right femur were excised	4
C	The proximal one-third of the shaft of the femur, including the head and both trochanters, was excised	4
D	The external capsule of the right hip was cut completely around and the ligamentum teres was divided	4
E	The external capsule of the right hip was cut all the way around, the ligamentum teres was divided, and the synovial reflection on the neck was circumcised and stripped down to the intertrochanteric line	4
	Total	20

Results.—The results of these experiments were similar to those in which young rats were used.

Group A—Resection of the cartilaginous head of the right femur, without injury to the epiphyseal line, did not interfere with longitudinal growth of the neck or of the shaft of the femur and the epiphysis did not regenerate.

Group B—After excision of the head and part of the neck of the right femur, the trochanter and shaft dislocated upward. Subsequent roentgeno-

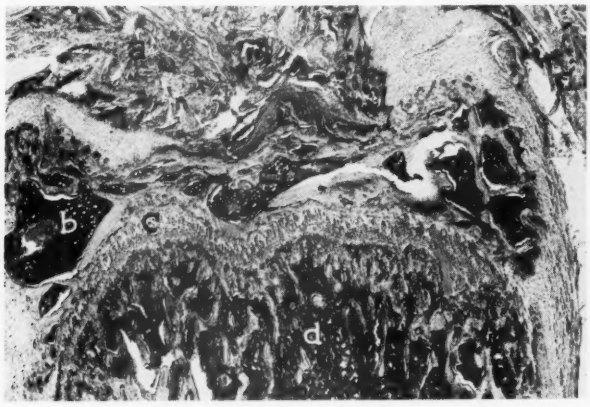

FIG. 3.—Photomicrograph of the distal end of rat femur nine weeks after subtotal resection of the epiphysis, showing fibrous tissue of repair (a) but no regeneration of articular cartilage. Normal longitudinal growth of metaphysis (d) is occurring through intact epiphyseal plate (d). (×30)

graphic and gross and histologic studies failed to reveal any evidence of regeneration of the head or of the resected portion of the neck. At necropsy, the proximal end of the neck was found to have healed over with dense fibrous tissue. The neck failed to develop, but longitudinal growth of the femoral shaft continued from the greater trochanter. In one experiment, 56 days after operation, the distance from the tip of the greater trochanter to

the intercondylar notch of the femur showed shortening of only 2 Mm. (Fig. 5 A), as compared to the opposite side.

Group C—Excision of the proximal third of the shaft of the femur, including the head, neck, and both trochanters, produced almost complete loss of function in the extremity. However, the distal two-thirds of the

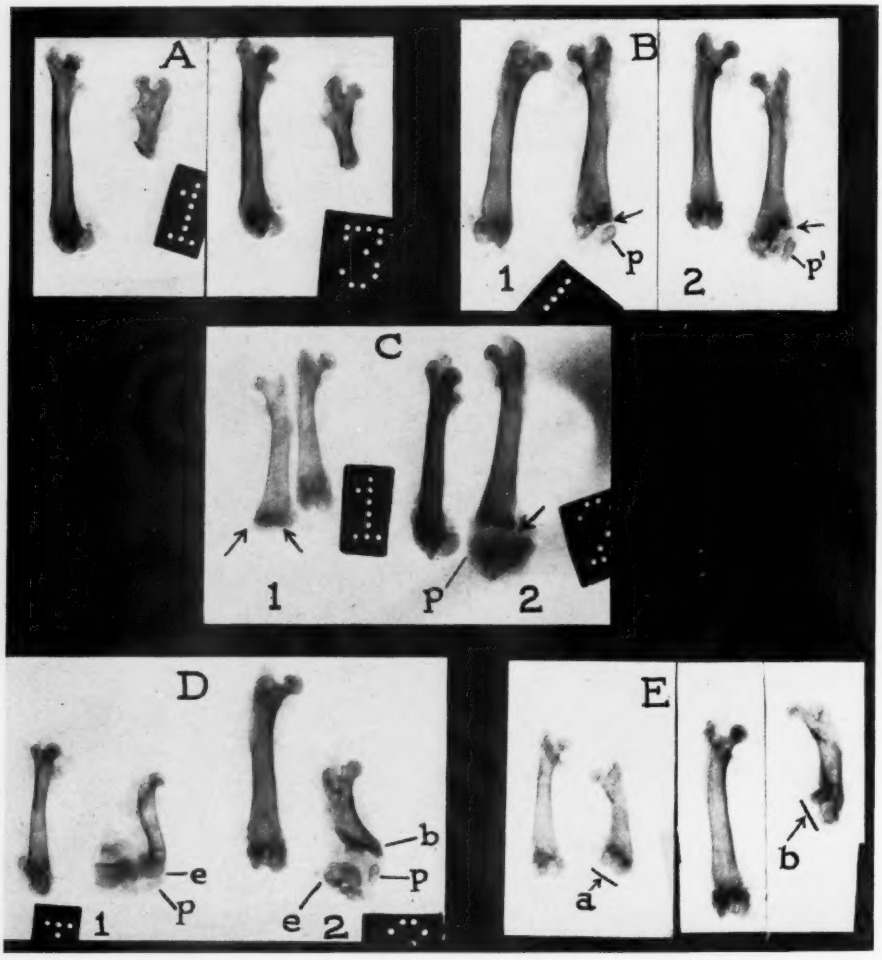

FIG. 4.—A. Roentgenograms of rat femurs showing repair of amputation stumps nine weeks after operation. The markers, small sections of hypodermic needle stylets, indicate that no longitudinal growth has occurred from the fibrocartilaginous cap which formed early over the resected end of the femur.

B. Roentgenograms showing the defect resulting from lateral subtotal hemiexcision of the distal femoral epiphysis nine weeks after operation, with the shadow of the patella (p) partly overlying same. The notch on the lateral side of the metaphysis of Rat 2 resulted from surgical trauma to the epiphyseal plate.

C. Illustrates the result of subtotal excision of the distal femoral epiphysis. In Rat 1 (four weeks) and in Rat 2 (nine weeks after operation) there has been no shortening of the diaphyses, but the epiphyses show no evidence of regeneration. Patella of Rat 2 is indicated (p).

D. Complete excision of the distal femoral epiphyseal plate resulted in growth arrest and marked shortening. After four weeks (Rat 1) the epiphysis (e) was fused to the diaphysis. A faint shadow of the patella (p) may be noted. In Rat 2, after nine weeks, the epiphysis remained ununited and the end of the shaft healed with well-formed bone (b).

E. Rat femurs showing deformity (a) four weeks (b) nine weeks after excision of the mesial portion of the distal epiphyseal plate. The condyles are tilted obliquely and there is marked shortening due to immediate growth arrest from the medial, and later, but still prematurely, obliteration of the lateral portion of the growth disk.

femur developed in length and breadth to a surprising degree, approximating that of the normal. In one experiment, after five months (Fig. 5 B), the diameter of the shaft in the distal one-third of the femur was essentially the same as that of the control side and the condyles of the femur were well developed. The proximal end of the shaft of the femur was found to have healed over with well-organized bone, resembling a conical amputation stump.

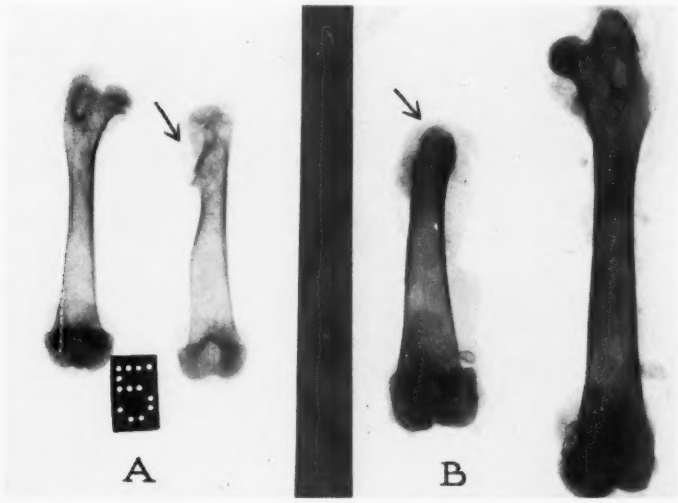

FIG. 5—A. Roentgenograms of the control and operated femurs of a rabbit 56 days after excision of the head and proximal portion of the neck of the femur. There has been no regeneration of the capital femoral epiphysis. Longitudinal growth of the shaft has continued from the greater trochanter epiphysis, but there has been a loss of two Mm. in length, as compared with the control.

B. Six months after excision of the proximal one-third of the femur, including the head and both trochanteric epiphyses, the amputated end of the femur has healed across with well-organized bone. The condyles of the femur and the distal one-third of the shaft have developed to approximately a normal extent, but no longitudinal growth occurred from the cartilage of repair and no epiphysis was regenerated.

Group D—When the capsule of the right hip joint was cut completely around and the ligamentum teres divided, no definite interference with the growth of the head and neck of the femur could be demonstrated. These dislocated upward, but the femur continued to grow at a rate comparable to that of the control side (Fig. 6 A).

Group E—When, in addition to cutting the capsule all the way around and dividing the ligamentum teres, synovia and capsular attachments were stripped from the metaphysis, *i.e.*, neck, down to the intertrochanteric line, gross deformity occurred. This was characterized by flattening of the head with shortening of the neck and what, roentgenographically, appeared to be bone absorption in the neck. After 46 days, the tip of the greater trochanter was found to be above the level of the acetabulum, the mesial side of the neck shortened, and there was marked coxa vara (Fig. 6 B). The appearance of this femoral head and neck is similar to Legg-Calve-Perthes' disease and is indicative of aseptic bone necrosis.

Discussion.—The results of these experiments may be interpreted as refutation of the conclusions of Selye with regard to the regeneration of a functioning cartilage plate which might contribute to the longitudinal growth of the bone following amputation in very young animals. There was bony closure of the medullary cavity of the resected end, which became rounded

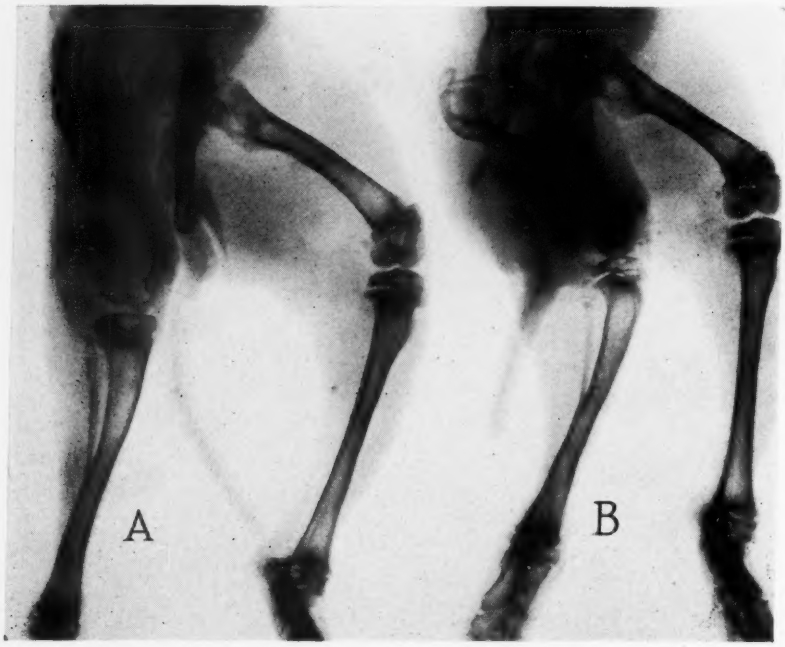

FIG. 6—A. Roentgenograms of pelvis and lower extremities of a rabbit 46 days after sectioning the capsule of the hip joint and division of the ligamentum teres. The hip was dislocated upward, but the two femurs are the same length. The head and neck of the femur have continued to grow and have maintained a normal relationship with the shaft.

B. Roentgenogram of a rabbit 46 days after section of the capsule and ligamentum teres and *extensive stripping of synovia and soft tissue attachments* from the neck to the intertrochanteric line. The flattened head, shortened neck, and areas of absorption in the metaphysis suggest Legg-Calve-Perthes' disease, indicative of aseptic bone necrosis.

or conical in contour. The remaining shaft did increase in length by growth from the other end, and Mullen and Gatewood[2] have shown that overgrowth may even occur at that epiphyseal line.

These studies further indicate that excision of the epiphysis, including the articular cartilage, but without trauma to the epiphyseal cartilage plate, is followed by slight bony regeneration, but no articular cartilage and there is no further longitudinal growth of the epiphysis. However, it causes no disturbance of longitudinal growth of the diaphysis.

This is evidence, although incomplete, which adds confirmation to the hypotheses of Nussbaum,[3] Peyton,[4] and Siegling,[5] that the articular cartilage serves as a longitudinal growth cartilage for the epiphysis and is to the epiphysis what the epiphyseal junction cartilage is to the diaphysis. Since the articular surface is covered by hyaline cartilage, these results conform to the generally accepted theory which is to the effect that hyaline cartilage,

destroyed, does not regenerate, but is replaced by fibrous connective tissue or fibrocartilage, neither of which can function as centers of growth.

Haas[6] demonstrated that it is possible to curette out the ossification center of an epiphysis without seriously affecting either the growth of the shaft or of the epiphysis and in such cases this center of ossification reforms.

Banks, Krigsten, and Compere[7] have recently reported the regeneration of epiphyseal ossification centers in young children following their destruction by pyogenic (four cases) or tuberculous (one case) infection, but in whom there had been preservation of varying amounts of their cartilaginous portions. In each case, longitudinal growth of the shaft continued, and indicated the remarkable degree of preservation of the growth cartilage disk in the presence of extensive infection within the epiphysis itself.

Loss of any portion, however, of the epiphyseal cartilage plate from injury results in partial to complete growth arrest with the development of deformity and shortening of the involved extremity. If only a portion of the plate is experimentally removed, a bony bridge forms, producing prompt growth arrest at this point with gradually decreasing activity of the remaining untraumatized junction cartilage, until it, too, undergoes premature fusion. In each instance in which the epiphyseal plate was the focus of surgical attack, it was definitely shown, confirming previous reports by Haas, that this epiphyseal cartilage plate possesses no capacity for regeneration.

CONCLUSIONS

(1) An epiphysis which, microscopically, contains the elements of a growth cartilage plate and which has the power to contribute to the longitudinal growth of bones is not regenerated after complete excision in very young rats or rabbits. Cartilage forms in the repair of the end of the stump, but disappears when the repair is complete.

(2) The entire longitudinal growth of the remaining segment of a long bone after excision of one end, as in the case of amputation, occurs entirely from the remaining epiphysis at the other end.

(3) Subtotal resection of all or one-half of the epiphysis is followed by slight regeneration of the bony center, but no regeneration of epiphyseal or articular cartilage and there is arrest of longitudinal growth of that portion of the epiphysis.

(4) Following injury or resection of the epiphyseal cartilage plate, the longitudinal growth of the shaft is either partly or completely arrested. If completely arrested, epiphyseodesis is established.

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INFUSIONS OF BLOOD AND OTHER FLUIDS VIA THE BONE MARROW IN TRAUMATIC SHOCK AND OTHER FORMS OF PERIPHERAL CIRCULATORY FAILURE *

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IN FAILURE of the peripheral circulation resulting from various causes, the administration of plasma or blood is often of great benefit. When the circulatory depression is marked and of some standing it is difficult to introduce any substances into the circulation by the venous route. Several factors operate to create this difficulty. The diminution in blood flow, which in certain vessels almost amounts to stagnation, renders it difficult to bring out the peripheral veins by the usual methods. The peripheral veins themselves are collapsed because of the reduced blood volume and poor venous return. If venesection is attempted, it is sometimes, even then, not possible to enter the veins, the walls of which may be in close apposition. Even when the vein is entered, one may not be able to inject fluid rapidly; the sluggish column of blood ahead prevents a rapid drainage of injected material with the result that further forceful injection may lead, especially in children, to a "blowing out" of the vein at the puncture site. All these difficulties which are the result of peripheral circulatory failure also interfere with any attempts at re-establishing the level of the blood volume, thereby helping to perpetuate the vicious circle. Attempts to re-establish blood volume other than by the *direct* introduction of fluids into the circulation fail, because of the markedly slow absorption of such fluids by the tissues, under these abnormal conditions.

During a stage when fluids are most urgently needed, one is left without ready access to the central portion of the circulation. It has occurred to us that, under such conditions, the bone marrow offers the ideal site for the introduction of fluids until the patient has reached such a stage that the peripheral circulation is restored and access to the veins is again possible. Since the marrow veins are surrounded by a rigid envelope, they are less likely to collapse, and can probably withstand forcible injection without overdistention and leakage better than the poorly supported peripheral veins.

Substances injected into the bone marrow cavity are taken up immedi-

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ately into the venous circulation apparently unchanged.[1] This method for giving fluids has been used in 72 patients to date, without any local or constitutional reactions.[2, 3] Experience with the method in animals having failure of the peripheral circulation due to hemorrhage[3] or in those undergoing an insulin reaction[1] impressed us with the desirability of widening the application of this method to the commonly encountered states of acute peripheral circulatory failure as observed in the operating room, in obstetric practice, in accidents, in industrial life or on the battlefield. Since our experience is limited to such incidents as are encountered in general hospital practice, this report is intended to draw the attention of those in whose hands the method may find a greater application.

Fate of Colored Solutions Injected into the Marrow Cavity of the Sternum.—If 10 cc. of green vinylite solution (a plastic material which solidifies on exposure to the air) are injected into the manubrium of the intact cadaver of an adult man, the solution leaves the marrow at once, enters the internal mammary veins and most of it is found in the form of a rubbery mass in the right auricle. The accompanying figure (Fig. 1b) illustrates the path traversed by the solution after it is injected into the sternum. Injection of dyes into a cadaver can give only an approximate idea of their spread during life, because of the absence of the circulation. The quick appearance of the dye in the auricle, however, serves to demonstrate the comparatively short distance between the sternal marrow and the right side of the heart. Rapid introduction of fluid into this side of the heart, therefore, may help to restore cardiac output during acute peripheral circulatory failure, by increasing the volume of blood returning to the central portion of the circulation.

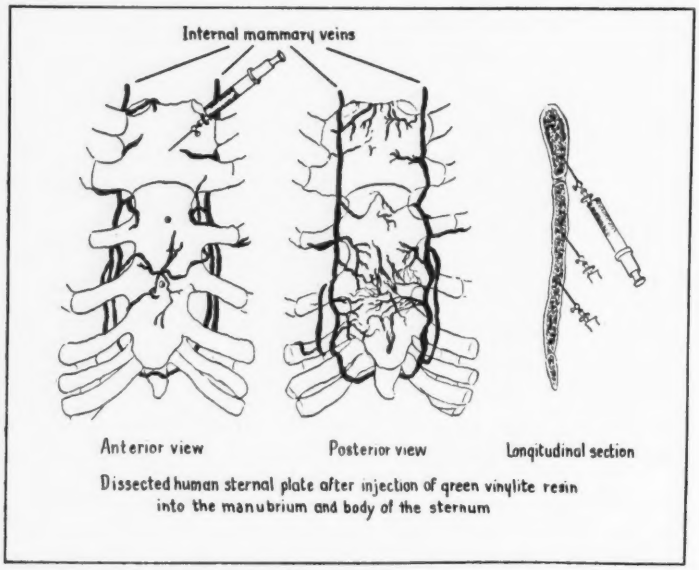
Internal mammary veins
Anterior view
Posterior view
Longitudinal section
Dissected human sternal plate after injection of green vinylite resin into the manubrium and body of the sternum

Fig. 1a (For Fig. 1b and legends see opposite page) →

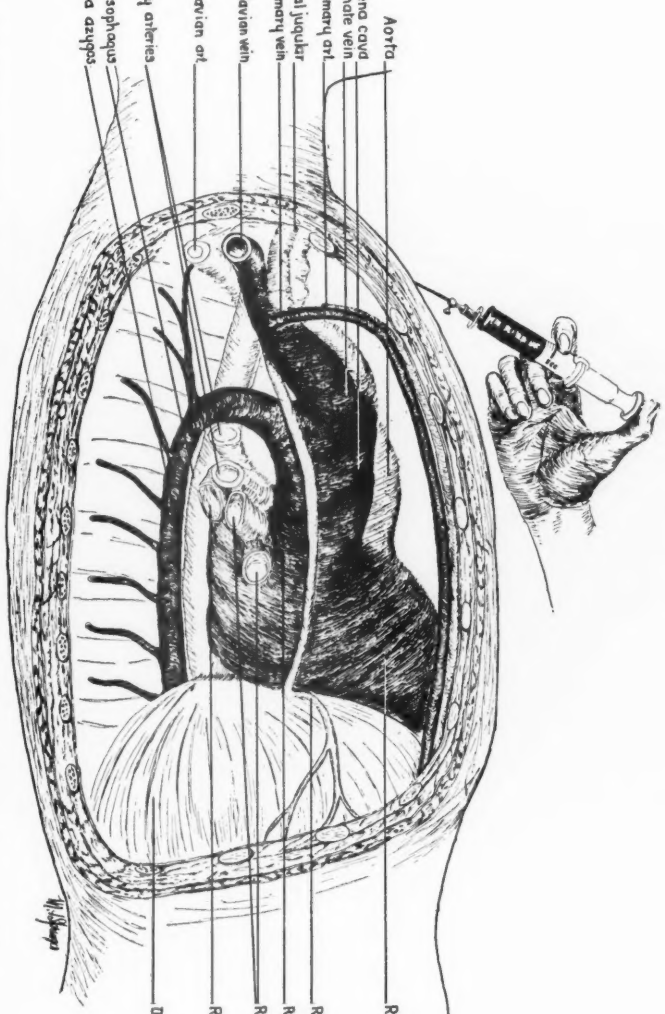

Fig. 1b

Fig. 1b—Right parasternal section of the thorax of an adult man (right lung removed). The path traversed by a green dyed solution injected into the sternal marrow cavity is indicated by the shaded vessels. Note the filling out of the vena azygos and intercostal veins, a result perhaps of the lack of resistance offered after death by the blood in that vein, and the absence of the sucking action of the right auricle.

Figure 1a (see illustration opposite page) illustrates the distribution of the dye in the retrosternal veins and the location of the needles during the injection.

Technic.—Details of the technic for introducing fluids into the sternal marrow have been described at length elsewhere.[2, 3] Only such variations in technic that may be applicable in patients with peripheral circulatory failure will be mentioned here.

After the needle has been introduced into the sternum (or tibia) and marrow has been obtained by aspiration, the syringe containing the material to be administered is inserted into the needle and the material is injected as fast as the resistance offered to it will allow. In conscious adult patients, rates of injection over 20 cc. a minute are usually accompanied by an unpleasant feeling of fulness in the sternum which passes off immediately after cessation of the injection. If it is contemplated to inject more than 50 cc. of fluid, much time may be saved by using a manually operated two-way stopcock with two thin-walled rubber tubes, one leading into the needle by means of an adapter and the other tube leading into the reservoir holding the blood, plasma or whatever fluid is to be injected (Fig. 2). By this means, it becomes unnecessary to remove the syringe from the sternal needle every time it has to be filled. If it is felt that a more rapid rate of injection is desirable than that obtained by using a single needle, two needles may be inserted at once in the sternum, one in the manubrium (above the angle of Louis) and the other 5 cm. below it, in the body of the sternum. Since the marrow cavity of the manubrium and the body of the sternum seldom communicate, it is possible to inject material through an orifice in the manubrium without its coming out of another orifice made in the body of the same bone. Care should be taken,

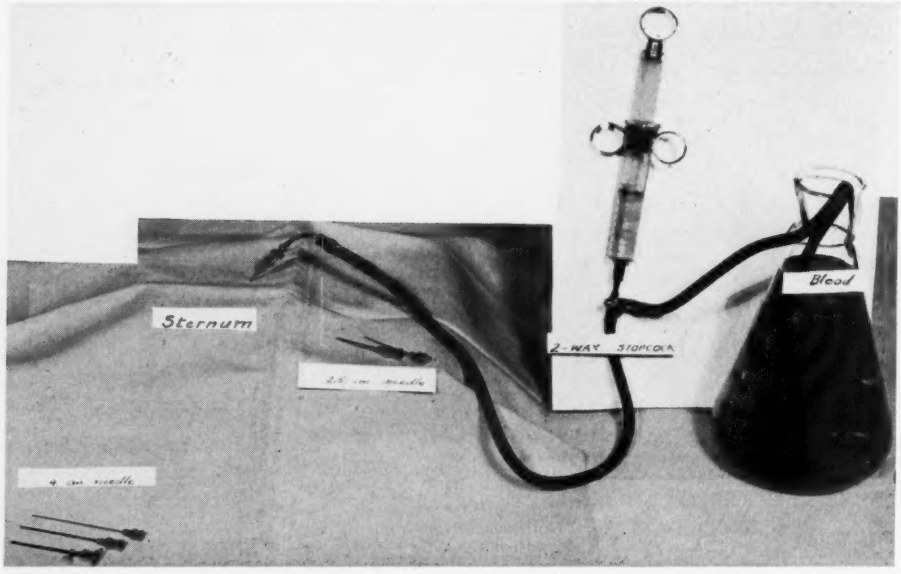

FIG. 2.—Arrangement for the rapid injection of fluids via the bone marrow. The blood may be put in a burette or inverted flask held above the level of the syringe, thus making easier to aspirate blood into it. All connections must be tight. A set such as the above, including two complete marrow infusion needles (4 and 2.5 cm. long respectively), sterilized, may be held in readiness in the central hospital sterilizing rooms or in emergency stations, for use at once when needed.

however, not to have both orifices made in the same portion of the sternum unless the fluid is going in with the same pressure through both of them. After the injection of the fluid is completed, the needle may be connected with a standard gravity infusion apparatus. If the patient has reacted from the state of collapse and the blood pressure has risen to a normal level, it may then be possible to use the peripheral veins.

The following cases illustrate the type of acute emergency in which this method finds its greatest usefulness:

Case 1.—(From the service of Dr. George J. Boines, Wilmington General Hospital, Wilmington, Del.) R. S., a white girl, age nine, had her tonsils removed on August 26, 1941, and went home the following day, apparently in good condition. On August 30, about 10 P.M., she began to vomit large amounts of blood and a few clots. During that day the child had been unable to eat anything because of pain in the throat. When admitted to the hospital she was having some bleeding in the postnasal space where a few large clots were observed. After the clots were removed, it was seen that the bleeding came from the posterior pharyngeal wall and was apparently controlled by packing. During the night the child began to bleed again and vomited many clots. Packing was again resorted to and seemed to control the bleeding. At 2:30 A.M. the child's condition became worse. She was cold, pale, and her skin was clammy. Her pulse was 170, weak and thready and her respirations 48. Stimulation was given and an attempt was made to give fluids intravenously but the veins of both arms and legs were collapsed and it was not possible to distend them by the usual methods. When, after repeated trials, it was felt that it was impossible to introduce a needle into any of the veins, the blood was given through the sternum using a marrow infusion needle. After aspirating a slight amount of blood from the sternum, the donor's blood was given through the needle. Three hundred cubic centimeters of citrated blood were infused followed by 200 cc. of normal saline solution, in two hours and 50 minutes. At 9 A.M. her temperature was 102° F., pulse 116, respirations 26. There was marked clinical improvement after the transfusion and the child was discharged three days later in good condition.

Case 2.—(From the service of Dr. Garfield Duncan, Pennsylvania Hospital, Philadelphia, Pa.) E. W., a diabetic colored woman, age 25, was in a deep coma when first observed by us. The blood sugar was 530 mg. per 100 cc. of blood. Attempts had been made to give insulin and fluids intravenously but, since the veins were collapsed, it was not possible to do it. The patient had been given several injections of insulin intramuscularly, apparently without effect. At 9 A.M. of December 30, 1940, a needle was inserted in the manubrium of the sternum and a small amount of blood-marrow mixture removed. At 9:02 A.M. 120 units of crystalline zinc insulin were injected followed by an infusion of 1,000 cc. of 5 per cent glucose at the rate of 11 cc. per minute. At 9:16 the pulse was felt at the wrist and five minutes later it was 96 per minute, regular and of fair volume. The patient came out of the stupor and answered questions. The infusion of 5 per cent glucose was continued at the regulated rate of 8 cc. per minute until the patient had received 1,500 cc. in about three hours. By 11 A.M. her circulation again began to fail but through a misunderstanding the insulin was given intramuscularly instead of through the sternal needle. She died at 12:15 P.M.*

Case 3.—(From the service of Dr. Frank R. Lock, Bowman Gray School of Medicine, Baptist Hospital, Winston-Salem, N. C.) M. H., age 45, female, white. On September 3, 1941, at 8:30 A.M. this patient underwent a perineorrhaphy and abdominal hysterectomy, under pontocaine spinal anesthesia. The operation proceeded without any complications. The patient's blood pressure was well maintained throughout, and she returned

* This case was previously reported in greater detail in Surg., Gynec., and Obst., 73, 281, September, 1941.

to her room in good condition. Between 9:45 A.M. and 1 P.M. her blood pressure declined gradually until at 1:15 a reading could not be obtained. There was no evidence of hemorrhage anywhere. At 1:30 P.M. it was possible to start an intravenous infusion of 10 per cent glucose (1,000 cc.) and 250 cc. of plasma. The impression was that the patient's peripheral circulatory collapse was probably due to pontocaine. The blood pressure remained low until the end of the infusion at 3:30 P.M. At 4 P.M. it was not possible to re-enter the veins and an infusion of 500 cc. of blood and 500 cc. of 5 per cent glucose was started through the manubrium of the sternum. While the infusion was flowing in by gravity the blood pressure dropped to zero. At this point the infusion apparatus was removed and the blood and glucose were injected through the sternum with a syringe. Between 5 and 5:20 P.M. 400 cc. of blood, 250 cc. of plasma and 500 cc. of 5 per cent glucose were injected through the sternum (total amount: 1,150 cc. in 20 minutes, or 57.5 cc. per minute). Administration of the fluid was continued by slow drip afterwards. Two doses of digifoline (five cat units) were then injected through the sternal needle. By 8:20 P.M. there were still signs of circulatory collapse, the abdomen was tense, the patient quiet and there was on palpation definite evidence of intra-abdominal hemorrhage. At 8:30 P.M. the patient was taken to the operating room and the abdomen was reopened under light ether anesthesia. There was a large amount of blood in the abdomen, coming apparently from the right broad ligament. While the vessel was being located and tied the circulation was maintained by injecting 500 cc. of blood through the sternal needle. At the end of the operation the blood pressure was 140/80; it was then possible to give 1,000 cc. of blood intravenously (Fig. 3).

Case 4.—(Reported by courtesy of Dr. Albert Davis, Camden, N. J.) M. McG., female, white, age 32, had a large pelvic abscess which ruptured while she was being moved to the hospital on October 30, 1941. At 2 P.M. of that day a celiotomy was performed; there was extensive lower abdominal peritonitis. Cigarette drains were inserted and 8 Gm. of sulfanilamide were left in the abdominal cavity. Immediately after the operation a transfusion of 500 cc. of blood intravenously and 1,000 cc. of salt solution by hypodermoclysis were given. Her condition was fair then, but by late afternoon of the next day the patient was in profound circulatory collapse; the pulse was 148, scarcely felt at the wrist, the skin was clammy, the lips cyanotic. Attempts to give her fluids by vein were unsuccessful for several hours; finally a needle was inserted into the vein but after 75 cc. of blood was given no more would run in. A marrow infusion needle was then inserted into the sternal manubrium and 425 cc. of blood was administered by gravity over a period of 75 minutes. This was followed by 250 cc. of 10 per cent glucose solution and 1,000 cc. of 5 per cent glucose, or a total of 1,675 cc. over a period of 13 and one-half hours. At the conclusion of the intramedullary infusion the patient was visibly improved and it was then possible to administer all subsequent fluids intravenously. For the following five days the patient's condition was critical but there were no more episodes of acute circulatory collapse and it was possible to give all further intravenous therapy without difficulty.

COMMENT.—Much of the medication given at present to patients with acute failure of the peripheral circulation is ineffective because it is administered by intramuscular or subcutaneous injection. Fluids, rapidly administered intravenously, are often the only means of restoring the circulation to normal. Though these principles are generally recognized, execution of the indicated measures is often made difficult or impossible by the very disorder of the circulation which requires treatment. Under these circumstances, the delay involved in locating a vein and in the attempts to introduce a needle into it, may jeopardize any chances for recovery from the acute circulatory collapse. When all required equipment is available and ready, it should be possi-

ble to start an intramedullary infusion or injection within less than three minutes after penetration of the skin by the needle. In contrast with venesection no incision of the skin or any special after-care of the wound is necessary; no veins are ligated, thereby depriving the patient of their use at some future time.

The method may be useful in the emergency treatment of mutilated patients or in those whose skin has been burned so widely as to make it impossible

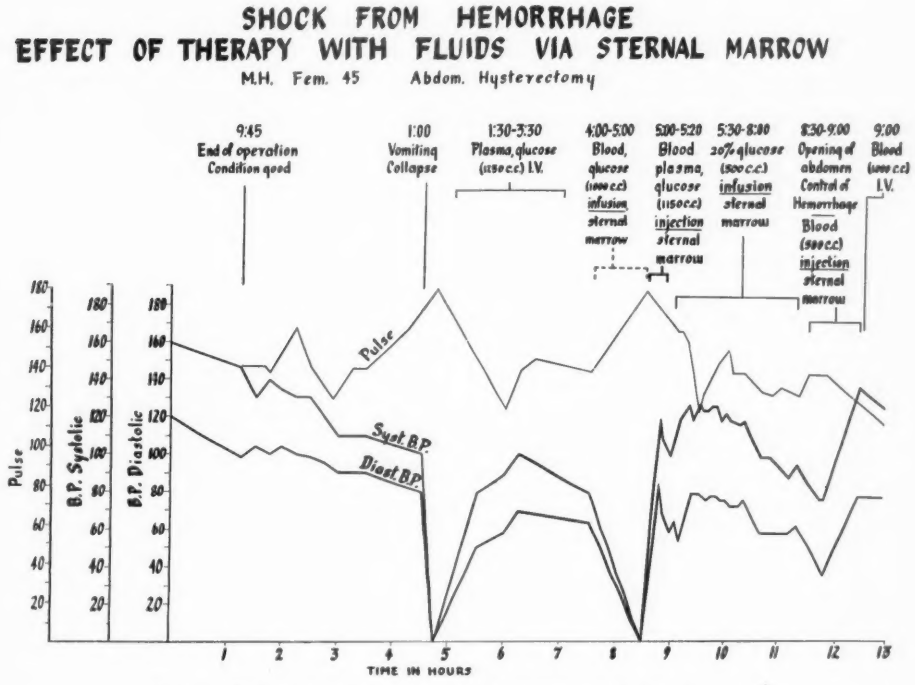
SHOCK FROM HEMORRHAGE
EFFECT OF THERAPY WITH FLUIDS VIA STERNAL MARROW
M.H. Fem. 45 Abdom. Hysterectomy
9:45 End of operation Condition good
1:00 Vomiting Collapse
1:30-3:30 Plasma, glucose (1150 c.c.) I.V.
4:00-5:00 Blood, glucose (1000 c.c.) infusion sternal marrow
5:00-5:20 Blood plasma, glucose (1150 c.c.) injection sternal marrow
5:30-8:00 20% glucose (500 c.c.) infusion sternal marrow
8:30-9:00 Opening of abdomen Control of Hemorrhage
Blood (500 c.c.) injection sternal marrow
9:00 Blood (500 c.c.) I.V.
Pulse
B.P. Systolic
B.P. Diastolic
Syst B.P.
Diast B.P.
TIME IN HOURS

FIG. 3.—Changes in the pulse and blood pressure of M. H. (Case 3).

to use the veins of the extremities. Since the needle, once in place, remains fixed, it allows continuation of an infusion while the patient is being transported from one place to another, without fear of displacing the needle.

Even though one is working under pressure of the existing situation, the precautions enumerated in detail elsewhere[2, 3] should be strictly observed. No fluid should be injected unless marrow is clearly obtained by aspiration. Sturdy needles, preferably especially made for the purpose, should be used to minimize the danger of bending or breaking. Familiarity with the anatomic landmarks should be obtained by practice on a fresh cadaver.

SUMMARY

In four patients with acute failure of the peripheral circulation, the injection of blood, fluids or drugs via the bone marrow was followed by a prompt recovery from the state of collapse. The intramedullary route is indicated

whenever veins are not available and a rapid introduction of fluids into the central circulation is urgently needed.

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BRIEF COMMUNICATIONS AND CASE REPORTS

ARTERIAL EMBOLECTOMY

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THE SUCCESSFUL REMOVAL of an arterial embolus is sufficiently unusual to warrant its report.

The most common source of embolization of the arteries is conceded to be the left side of the heart.[1, 2, 3] About 50 per cent of the cases are associated with mitral disease.[3] The localization of the embolus is most frequently in the common femoral artery. The case related below illustrates the value of heparin and passive vascular exercises (pavaex treatment) when combined with embolectomy.

Case Report.—Hosp. No. 40-1875: A. E., white, female, age 31, was admitted to the Medical Service of the hospital, June 17, 1940, complaining of abdominal pain, nausea, and vomiting of three days' duration. She was a known cardiac for four years, but had been without treatment for seven months prior to her admission. Physical examination revealed the heart enlarged to the left, with a presystolic and diastolic thrill at the apex. The patient was fibrillating at a rapid rate. There were numerous moist râles at both lung bases. The liver was moderately enlarged and tender. There was no peripheral edema. The diagnosis at this time was rheumatic heart disease, with mitral stenosis and insufficiency, and auricular fibrillation. The patient's heart rate did not slow with digitalis. She was then placed on quinidine and the rate dropped markedly.

On June 25, 1940, the patient complained of coldness and pain in both calves and numbness of her entire left lower extremity. Physical examination at this time revealed absent pulsation of the dorsalis pedis artery. Two days later, the pain in her left calf and foot became more severe. The dorsalis pedis artery presented no pulsation and the pulsation of the popliteal was hardly perceptible. Her left leg from the knee down was numb and sensation was absent. The leg became cyanotic and cold. There was a faint pulsation at the femoral artery just below Poupart's ligament. In view of this evidence, the patient was transferred to the Surgical Service that night, and an arterial embolectomy was performed by one of us (F. W. B.).

Operation.—Under local anesthesia, an incision was made along the inner aspect of the left thigh in the upper one-third of the course of the femoral artery. The femoral artery was visualized and was found to be in spasm and not pulsating. Stay-tags were put around it to control bleeding and the vessel was opened. It did not bleed on opening. A fine suction tube was inserted and suction applied. There was no blood or clots removed from the proximal portion of the artery. Some dark venous blood was obtained from the distal portion of the vessel. The incision was then extended upward and the femoral artery was inspected at a level, one inch below Poupart's ligament. There, the artery was found to be much more dilated and its walls were distended by thrombi. An incision was then made over this portion of the femoral artery. An organized thrombus was removed by forceps; however, active bleeding did not occur, so a glass tube was inserted to about the level of the bifurcation of the aorta and aspiration brought pieces of soft clot followed by active arterial bleeding. Immediately thereafter, pulsation started and continued down to the site where the artery was first incised. The wound was then

irrigated with heparin and the incisions of the vessel were closed by interrupted fine vaselined silk sutures. The skin incision was closed with Stewart stitches.

Postoperative Course.—Upon returning from the operating room at 1:30 A.M., June 28, 1940, the patient was given 30,000 units of heparin. This was repeated at 4 P.M. and 8:30 P.M. The next four days the patient was given 30,000 units of heparin per day. The heparin was given with normal saline, which was being administered by continuous intravenous drip at the rate of 3,000 cc. per day. On the day following the operation, the leg appeared a little warmer. The patient, however, complained of a great deal of pain. The entire limb was then inserted into a pavaex machine, after which the patient appeared to be more comfortable. The limb was kept in the machine for varying periods of time, from two to four hours, three times a day. The machine was set at two cycles per minute, with a positive pressure of 20 and a negative pressure of 60, so that the ratio of negative to positive pressure was 3:1.

On June 30, 1940, the foot appeared warmer than prior to operation, although still cooler than the other one. It was not quite as pale. The area of anesthesia extended to about five inches below the knee. There were no palpable vessels in the entire limb except the femoral artery. Examination three days later revealed sensation returning, and the foot was slightly warmer. However, it was still discolored, particularly over the heel. A sloughing area appeared above the anterior aspect of the knee where the rubber cuff of the pavaex machine had been applied. However, from this time on, the patient progressively improved so that she was discharged, August 15, 1940, in good condition.

It is not our purpose to completely review embolectomy of the vessels of the extremities. This subject has been well reviewed elsewhere.[1, 3]

The occurrence of an embolus induces a certain degree of spasm in the vessel wall involved. The drop in pressure distal to the point of occlusion further diminishes the caliber of the lumen. This, associated with the retarded blood flow, endangers the efficiency of the collateral circulation. When the embolus becomes adherent, it injures the intima; this favors coagulation of the blood. If this process continues, the extending clot may obstruct the collateral vessels.

The use of heparin as a physiologic anticoagulant is well outlined by Mason.[4] Best[5] has demonstrated how it prevents thrombosis. After embolectomy has been accomplished, failure to acquire a cure may be the direct result of secondary thrombosis. Murray[6] has demonstrated that heparin is nontoxic in humans; that it is useful in diseases complicated by intravascular clotting; and that it will prevent thrombosis and clotting in blood vessels.

Since its properties have been demonstrated, many successes have been reported following its use. Murray[7] reports 440 patients treated in the hospital with heparin in whom thrombosis and embolism did not occur. He also reports 12 successful embolectomies in which heparin was used. He suggests administering heparin at the time of operation and for three to four days following.

Herrmann and Reid[8, 9] have demonstrated the benefits derived from the pavaex treatment. This procedure can be carried out without discomfort or untoward effects.

We agree with Lund[10] that the best results are obtained when early

embolectomies are performed. Heanley[11] concurs in this opinion, but again emphasizes the advantages offered by heparin.

Burnett[12] performed a retrograde extraction of an embolus; however, without success.

SUMMARY

This case illustrates the successful removal of an embolus from the femoral artery, 48 hours after the onset of symptoms, by a retrograde suction procedure. The success is further attributed to the combined use of heparin and pavaex treatment.

We wish to thank Roche-Organon for supplying us with "Liquaemin" (heparin).

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AN APPARATUS FOR CLOSED DRAINAGE OF THE VENTRICULAR SYSTEM

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CHRONIC increased intracranial pressure has usually been combated by repeated tapping of the ventricular system or by continuous drainage into sterile gauze *via* a cannula or catheter left *in situ*. Both means of drainage, no matter what precautions are taken, submit the patient to a risk of sepsis. In order to avoid this hazard, a continuous closed system of drainage was devised. It is in no sense an original idea but merely an improvement upon various devices that have been employed in many clinics.

This apparatus has been successfully employed as a temporary means of decompression where block has existed caudad to the foramen of Monro. Its use is indicated when dehydration and inanition must first be dealt with by supportive measures before operation can be undertaken. It is further indicated when diffuse pressure clouds localization and ventriculography might prove to be too drastic as a first step in an investigation. The difficulties arising from edema in a partially removed malignancy and consequent block of the ventricular system occurring during a course of roentgenotherapy may often be surmounted by this type of drainage. It has further been of aid in judging the adequacy of skin for closure when removal of a large meningocele is contemplated in a case of arrested hydrocephalus. The meningocele may be gently collapsed, allowing an accurate estimation by manipulation of the surrounding skin. When excision of such a type of meningocele has been carried out and closure effected under any degree of tension or by undercutting, it has proved to be of value in preventing spinal fluid leakage from or extravasation beneath the wound.

*Description of Apparatus.**—The apparatus consists of a flanged, sterling silver cannula (A) which is blunt at the end, equipped with a stylet and threaded adaptor. Cannulae have been made up in the following lengths: 4, 5, and 7.5 cm. Light, transparent rubber tubing connects the adaptor with a "three-way" stop-cock (B) and in turn with a 250 cc. burette. The burette is closed with a tightly packed plug of gauze. Autoclaving is the preferable means of sterilization.

Operative Procedure.—Bilateral posterior parietal bur-holes are made under novocain anesthesia, with or without the support of avertin, depending upon the circumstances. After the dura and arachnoid are opened, a brain needle is used to determine the depth of the ventricle. With this knowledge, a cannula of suitable length may be chosen. The wounds are then closed in layers, using black silk throughout. The cannula with stylet in place is next

* The cannulae were made by George C. Gebelein, 73 Chestnut Street, Boston, Mass.

placed through the closed wound. As soon as the stylet is withdrawn, the adaptor is threaded into the cannula. A square of gauze, which has been slit to its midpoint, is placed between the flange of the cannula and the wound. Several similar squares are placed above the flange. Fluffs are then wound loosely about the lower 3 cm. of tubing in such a manner as to guard against contamination but yet avoid kinking or compression. The dressing is secured beneath a turban of woven bandage. This is, in turn, stabilized by a chin-strap of flannel secured at intervals with safety pins as far as the midline. The tubing is then looped beneath a small safety pin in order to avoid direct traction on the cannula. When the patient is placed in bed he should lie on the side opposite the cannula. The burette is hung on an adjustable arm at the head of the bed.

Should previously made bur-holes exist, novocain may be infiltrated and a small stab wound made down to the dura. The dura should be pierced by a No. 18 lumbar puncture needle, and enlarged by the passage of a brain needle, used in ascertaining the depth of the ventricle. The appropriate cannula may then be passed down this tract without trauma. The next steps have already been described. It is also possible to pass the cannula through widely separated sutures in order to establish drainage, if previously made bur-holes do not exist, or if the making of bur-holes is contraindicated.

Maintenance of Drainage.—The patients are afforded great subjective relief by this means of decompression. Judgment concerning restraint of the patient's arms must be made, depending upon the age and mentality of the individual. It is wise to bolster up all types and ages of patients on the side opposite the cannula to avoid compression or tension on the tubing. Doughnut-shaped rings of gauze and cotton are of use in stabilizing the head and protecting the dependent ear.

Cultures and cell counts are made bidaily. Fluid is withdrawn as often as the 100 cc. mark in the burette is reached, in order to prevent any possible contamination of the upper portion of the burette.

The toilet of the stop-cock is worth mentioning. Except when in actual use, a sterile gauze covering should be over it. Before withdrawing fluid for cell count and culture, the stop-cock is prepared with ether (3.5 per cent), iodine, and 70 per cent alcohol, applied in that order by means of saturated sterile swabs. Cell counts are taken after the first 5 cc. of fluid have been withdrawn. Cultures are taken after 25 to 30 cc. have been withdrawn, in order to prevent inhibition of any possible growth by antiseptic solutions used in the preparation of the stop-cock.

Seventy-two hours of drainage through one bur-hole is the maximum time advisable. Sepsis has not occurred within this time limit in our experience. A fresh apparatus may then be set up, using the other bur-hole if further drainage is necessary.

Approximately normal intracranial pressure may be maintained by adjusting the burette holder at the head of the bed at frequent intervals, in order to maintain the *in vitro* level of fluid at the level of the uppermost lateral

ventricle. In this manner, the patient is spared the sudden upsetting changes of pressure that occur when intermittent tapping is carried out.

In the hands of an alert house staff and competent nursing staff, this apparatus has been very easy to handle. Children seem to realize the benefit it affords them and seldom have revolted against it. Observation by nurses

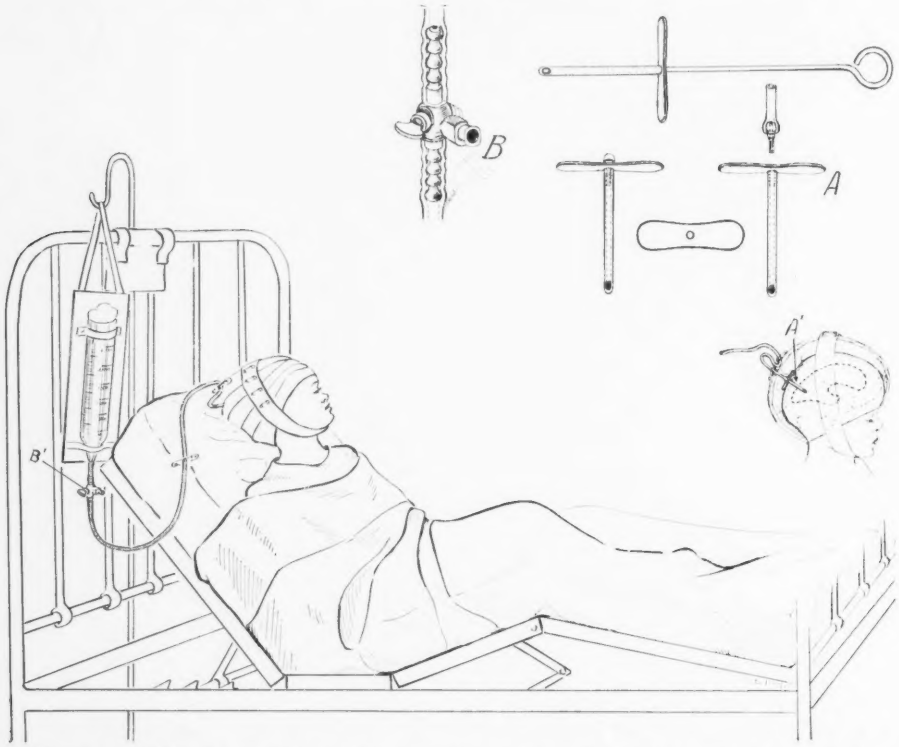

PLATE I.—Position of patient in bed with apparatus set-up. Note burette plugged with gauze hanging from an adjustable arm. A: Silver cannula with threaded adaptor and stylet. A1: Position of cannula in ventricular system and overlying dressing. B: "Three-way" stop-cock. B1: Position of "three-way" stop-cock in system.

at ten- to 15-minute intervals has proved to be sufficient to ward off any inequality of pressure or slipping of the well-bolstered patient from position which might jeopardize the continuity of drainage.

We have described this system of ventricular drainage thinking that it might be of aid to others.

AMPUTATION FOR OSTEOGENIC SARCOMA OF LOWER END OF FEMUR

NINE-YEAR FOLLOW-UP OF TWO CASES

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Case 1.—Hosp. No. 83115: H. S., age 16, was admitted to St. Luke's Hospital, November 24, 1930, with a history of swelling of the right knee of three months' duration steadily increasing. This became painful one month before admission and during this period the pain increased. Limitation of extension of the right knee developed and walking became more and more difficult. There was no preceding history of trauma. He had always enjoyed good health.

Examination showed a fusiform swelling from the knee to a point about 12 cm. up the femur. This was hard and seemed to involve the bone only and not the overlying soft tissues. No inguinal nodes were palpable. There was 30° limitation of extension of the knee joint.

Operation was performed one week after admission, under nitrous oxide anesthesia. A biopsy of the bone growth was taken and a frozen section was reported as osteogenic sarcoma. A high thigh amputation was then undertaken, and the flaps closed without drainage.

The postoperative course was exceedingly smooth and remarkably painless. The stump healed *per primam* and he was discharged on the twelfth postoperative day. He had no preoperative or postoperative radiotherapy.

Pathologic Examination.—Path. No. 40815: Dr. Leila C. Knox. The growth is largely of the spindle cell type but in many areas it shows the differentiation characteristic of periosteum. The nuclei are not extremely numerous, are elongated or triangular in outline, and there is considerable myxomatous material between the cells. There is also a moderate amount of collagen in very finely divided bundles. Between these are occasionally very large nuclei, indicating a far more malignant type of growth than some of the fibrous areas would suggest. In these large cells mitotic figures are occasionally to be seen (Fig. 1).

The lining of the large cavity in the bone consists of tissue of the same type as that forming the main tumor mass. Fragments of necrotic bone are included in this. The sections do not show any osteoid tissue, but the close resemblance to periosteum indicates its osteogenic derivation. (This case has not yet been registered with the Bone Sarcoma Registry.)

Case 2.—Hosp. No. 83108: S. G., male, age 22, was admitted to St. Luke's Hospital, November 21, 1930, complaining of pain in the inner lower right thigh, first noticed about eight months before admission. Two months later he found a "slight swelling of the bone" in this area. At first the swelling increased slowly, but for the last three months it had seemed to grow much more rapidly. There was no history of trauma preceding the appearance of the lesion. During the two weeks before admission, he was given three roentgen ray treatments over the site of the lesion, at Memorial Hospital. His previous history was negative except for the fact that he had had rheumatic fever at the age of 16.

Examination showed, on the medial aspect of the right thigh, just above the medial epicondyle, a bony tumor which was not tender and seemed definitely fixed to the underlying bone. The overlying skin appeared normal and moved freely over the growth. The growth was estimated to be about 3x7 cm. in size. Preoperative roentgenograms were not taken at St. Luke's as they had been made elsewhere. On the day after admission

a biopsy was taken of the growth. This was reported as an osteogenic sarcoma of the femur. Two days later, under nitrous oxide anesthesia, a high, right thigh amputation was performed, and the flaps were closed without drainage.

Except for a postoperative temperature of 104° F. on the first day after operation, which gradually dropped to normal in a week, his convalescence was smooth. The wound healed *per primam* except for moderate drainage of serum, and the patient left the hospital three weeks after the operation.

Pathologic Examination.—Path. No. 40796: Dr. Leila C. Knox. The growth is derived from the periosteum and is characterized by the formation of large quantities of

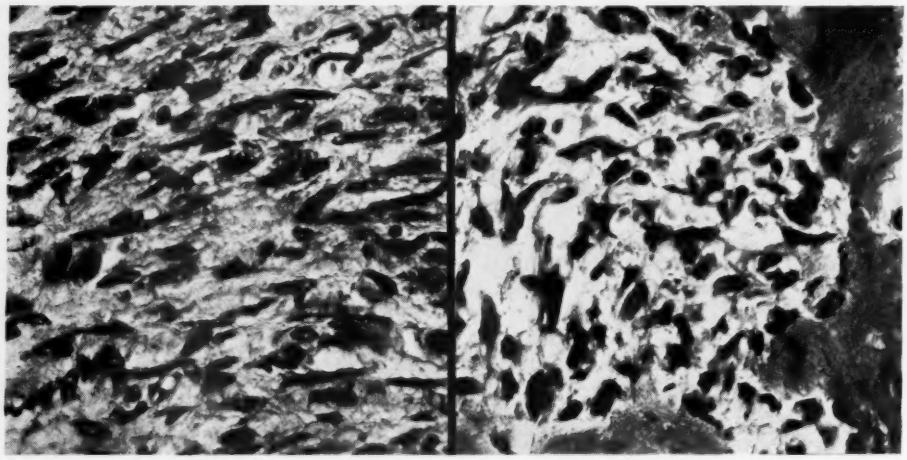

FIG. 1. FIG. 2.

FIG. 1.—Case 1: Photomicrograph showing the predominant type of growth. Large periosteal fibroblasts are arranged in a slightly laminated manner, but differ from each other in size and shape, and all of them are larger and more irregular than normal cells. Structures resembling bone cells are seen occasionally. Osteoid tissue is not included in this section. (×750.)

FIG. 2.—Case 2. Photomicrograph showing the tumor to be composed of large connective tissue cells, very irregular in size, shape and arrangement, many of them surrounding newly formed osteoid areas. An occasional bone cell is included. (×750.)

bone in a moderately cellular connective tissue matrix. Some of these areas are extremely vascular, containing large blood sinuses, and around these bone is forming in small quantities. In some places the walls of these sinuses are not lined with endothelium, but only with a connective tissue type of tumor cell. There is only a little old pigment, but some of the sections show numerous endothelial giant cells. There are also osteoclasts which may be distinguished from the phagocytic cells. In some areas the connective tissue is myxomatous and differs little from the normal. In others, it is distinctly cellular while in still others the nuclei are irregular, large and aplastic. The growth is composed of about equal parts of osteoid tissue and of spindle cell connective tissue, and is unquestionably malignant (Fig. 2). (This diagnosis has been confirmed by Dr. Francis Carter Wood, but has not yet been registered with the Bone Sarcoma Registry.)

He was readmitted January 24, 1936, four years ago, because of a lump in the stump, first noted by him ten days previously. Otherwise he had been entirely well. Roentgenograms of the chest were made and proved to be negative.

On the day after admission, under nitrous oxide anesthesia, an incision was made over the mass which he had discovered in the stump. This proved to be muscle which had apparently separated and retracted from its point of union with the other muscles in the stump. A biopsy of the muscle mass was made and reported "regenerative changes in muscle, no tumor in sections."

DISCUSSION.—DR. FRANCIS CARTER WOOD (New York): Doctor Wood said that, with reference to Doctor Solley's cases, one could use the old law term, "the thing speaks for itself." The extensive bone destruction and the morphology of the tumors is perfectly definite. On the other hand, Doctor Wood made the point that although the diagnosis was made in his own laboratory, a bad habit has grown up of making a diagnosis on most bone tumors and calling them "osteogenic sarcoma." In Doctor Solley's first case there was a periosteal spindle cell sarcoma, and it would have been better to have so named it rather than to have concealed the morphology under the general term "osteogenic sarcoma." The second tumor was rightly called osteogenic sarcoma, and interested Doctor Wood very much because of the fact that the surgeon of to-day is assuming a position of hopelessness in the treatment of these bone sarcomata. There is nothing to be accomplished by radiating them, inasmuch as osteogenic sarcoma, with cartilage production, is not susceptible to radiation. It is true that the salvage, even with prompt surgery, is small; but if one continues to attempt to salvage these with roentgenotherapy all will die. These two patients were snatched from inevitable death by fairly prompt and extensive surgery and constitute excellent illustrations of the situation.

GLOMUS TUMORS

REPORT OF FOUR CASES IN SAME FAMILY

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GLOMUS TUMORS have been recognized as a clinical entity since about 1912, when Wood, of Edinburgh, described several cases of "painful subcutaneous nodules" of the extremities. In 1924, Masson[1] published the first definite description of the pathologic and clinical characteristics of glomus tumors. He defined and described the histology and physiology of the normal glomus with a demonstration of the curious neurovascular muscular structure, and so established glomus tumors as definite entities. Since his classic paper, the lesion has been thoroughly investigated. An excellent and exhaustive description of the condition, with a review of the literature was published by Oughterson and Tennant[2] in 1939.

While it is known that glomus tumors may occur anywhere in the body, a study of the literature reveals only one case of the lesion in the thigh. The vast majority are to be found in the upper extremity—the hand, nails or the fingers. The glomus tumor has characteristic clinical signs. It is usually a small, superficial pigmented nodule exquisitely tender and painful. The nodule varies from a few millimeters to a few centimeters in size, always superficial, and since it is made up of blood vessels, pigmentation varies according to its depth from a deep purple to varying shades of red, which may even be almost absent in the common subungual type. The tumors are generally found on the extremities, commonly the upper and rarely on the face and trunk. Since the time of Masson, the subungual form has been the classic type but these tumors are now recognized in many other regions, two cases having recently been reported by Grauer and Burt[4] on the penis. The most characteristic sign is the peculiar severity of pain and tenderness, paroxysmal, agonizing throbbing and associated with modalities of unusual intensity by changes in position, heat or cold, *etc.*, and extreme sensibility to contact and pressure. These typical findings, varying in degree, should serve to establish at least a presumption of glomus tumor in the diagnosis of superficial vascular tumors (fibroma, angioma, varix and malignant tumors).

Clinicians have noted in the past that the lesions were often accompanied by the phenomenon of increased warmth throughout the affected area. This was not fully investigated however until 1937, when an excellent study was reported by Stabins, Thornton and Scott.[3] They showed that the increased

temperature was apparent in the entire limb and not restricted to the area of the tumor. Their suggestion was that the mechanism was one of vasodilatation of the peripheral vessels due to a reflex, the efferent arc of which is not limited to the peripheral nerve field in which the sensory stimuli arise. Thus it would seem that the vasodilatation is excited by sensory stimulation which acts on the trigger mechanism. This is unusual, in that the common effect of painful stimulation is one of vasoconstriction. It may be that the

FIG. 1.

FIG. 2.

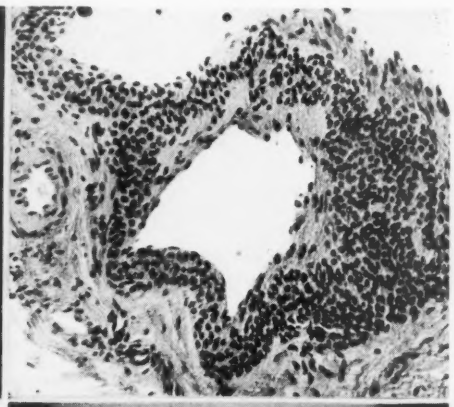

FIG. 3.

FIG. 4.

FIG. 1.—Case Mr. D.: Showing scar on thigh following removal of tumor.
FIGS. 2 and 3.—Case Mr. D.: Photomicrographs of lesion removed. (×400 and ×100, respectively.)
FIG. 4.—Case Mrs. J., age 31: Showing lesions on left upper arm.

nerve elements of the glomus are parasympathetic in nature or perhaps preganglionic sympathetic fibers. The surgeon should consider glomus tumor when dealing with a highly vascular, rather small tumor on the surface which presents severe pain and tenderness peculiarly out of proportion to the size, distinction and appearance of the lesion. All such tumors should be considered as possible glomus tumors and the final diagnosis made by the laboratory. It is quite probable that the tumor is not as rare as the literature would indicate. Many excellent clinicians are not familiar with the lesion

and many such tumors are no doubt overlooked or treated as varicosities, angiomata, *etc.*

Nothing has been suggested as to any familial tendency in this condition. In our study we are presenting four cases occurring in a single family. The distribution was as follows: (a) Paternal aunt—lesion on wrist. (b) Sister —four on upper extremity. (c) Brother—one on thigh. (d) Daughter of sister—one on lower leg.

Only one case came to operation—that of the brother, a medical student, age 22. He stated that the small discolored area in his thigh was noted when he was an infant. However, during the past eight years it had become more elevated and painful, the pain being sharp and of a cutting nature, especially when the lesion was touched. Examination showed a small bluish nodule, 2 cm. in diameter, on the anterior surface of his left thigh. This was removed surgically (Fig. 1) and the accompanying photomicrographs reveal the morphology of the tumor (Figs. 2 and 3). The other members of the family showed similar lesions with the same symptom complex. The sister (Mrs. J.), age 31, has three lesions in the region of the left upper forearm and lower arm, and one on the dorsum of the proximal phalanx or middle finger (Figs. 4, 5 and 6). The temperature readings on Mrs. J. were as follows:

Room temperature 71.5° F.

(a) Before immersion in cold water:		
Fingers	(right) 79.5° F.	(left) 87.4° F.
Palm	83.0° F.	88.0° F.
Wrist	83.8° F.	88.6° F.
(b) Five minutes following immersion:		
Fingers	(right) 74.6° F.	(left) 80.0° F.
Palm	79.2° F.	84.0° F.
Wrist	80.0° F.	84.0° F.

Readings on Ann J. were as follows:

Room temperature 67.5°F.

Right foot	76° F.
Left foot	72° F.

After irritation of the lesion the temperature of the right foot rose to 79° F.

SUMMARY

We have presented cases of glomus tumors appearing in four members of the same family. The sites of occurrence are rather varied. Temperature readings are presented in two instances, to illustrate the likelihood that the lesion produces temperature changes and that the glomus body exerts an influence in regulating surface body temperature. We feel that the lesion may not be as uncommon as supposed but that unfamiliarity with the condition by clinicians may have caused many tumors to be overlooked and incorrectly diagnosed. Facilities are usually available to most surgeons for recording surface temperatures, and in these tumors surface temperature readings offer diagnostic aid. This test determines that pain which is a prominent symptom of the lesion is associated with vasodilatation; we are reporting the occurrence of glomus tumors in four members of the same

family presenting widespread distribution of the tumors, all of which present, however, rather uniform and typical characteristics.

FIG. 5. FIG. 6.

FIG. 5.—Case Mrs. J., age 31: Showing lesion on dorsum of proximal phalanx of right middle finger.
FIG. 6.—Case Ann J., age five: Showing lesion on lower right leg.

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CENTRAL CHONDROSARCOMA OF THE FEMUR*

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CENTRAL CHONDROMATA, or chondromyxomata, are common lesions in the small bones of the hands and feet, the ribs, and spine. They are benign and usually single lesions. According to Geschickter and Copeland[1]: "True central chondromata of the long bones are extremely rare, and it is doubtful whether such a diagnosis is justified on the basis of the roentgenogram alone. In nearly 2,000 tumors of the bone there are but five well-established cases, and in these the resemblance is so close to malignancy in the roentgenogram, and the tendency for the lesion to recur and to be cured only by radical operation is so great, that there is little practical harm in classifying these tumors as forms of chondrosarcoma."

For treatment, they recommend curettement followed by adequate cauterization, either thermal, or chemical with 50 per cent zinc chloride. Recurrences in the case of large bones have followed this treatment in about 25 per cent. They advise postoperative radium therapy.

Case Report.—J. M., female, white, age six, was admitted to the Stuyvesant Square Hospital (now the Skin and Cancer Unit of the New York Post-Graduate Hospital) in December, 1933. She was said to have commenced to walk at 14 months and to have walked normally until about four years of age. Since that time, two to three years, she had had a left lower extremity limp which the child said was because it hurt her. For about one year before admission the parents had carried the child most of the time on account of the pain and limp. There was nothing relevant in family or past history.

Examination showed no abnormalities except the left upper thigh, which was considerably larger than the right, while the remainder of the extremity was smaller. On palpation the enlargement seemed to be bony, was smooth, not tender and with no inflammatory signs.

Roentgenologic examination showed a central lesion, involving the greater and lesser trochanters and extending three inches down the shaft of the femur. There was general expansion of the bone over this area with no break in the cortex except at one point where there was a suggestion of an incomplete fracture. The involved bone has translucent areas marked out by lines and particles of calcification which give it a multiloculated appearance. There is no evidence of periosteal involvement (Fig. 1). The whole skeleton was examined roentgenologically and no other lesion found. Wassermann and Kline tests were negative. Complete blood count, urine findings, and temperature were normal.

The diagnoses considered were Ewing's tumor, giant cell tumor, bone cyst, and osteitis fibrosa cystica. The case did not seem to conform to any of these.

Operation.—January 5, 1934: An incision was made over the great trochanter. Nothing abnormal was encountered in the soft parts. Through a small opening in the cortex, which was not over one-sixteenth of an inch thick, tissue was removed for frozen section. Grossly and microscopically, this seemed to be cartilage. A larger window was then made on the outer aspect of the great trochanter and bluish-gray, firm material was curetted out readily until apparently firm bone was felt on all sides. A cavity about 4x1½x1½ inches was left involving greater and lesser trochanters, part of neck, and

* Presented before the New York Surgical Society, December 6, 1939.

upper third of shaft. No cauterization was undertaken and no bone chips were inserted. The periosteum and soft parts were sutured and a plaster spica applied.

Pathologic Examination.—Microscopic: Dr. D. S. D. Jessup. Islands of cartilage with large cell spaces and a hyaline matrix, separated by small areas of fibrous tissue. At one point scattered giant cells of foreign body type are found. The decalcified sections show thin layers of bone forming in trabeculae along the edges of the islands of cartilage. There are a few osteoclasts (Figs. 2, 3, and 4). The essential growth seems to be chondroma. *Pathologic Diagnosis:* Osteofibrochondroma.

Subsequent Course.—The plaster spica was kept on for four and one-half months. It was then believed that there was sufficient bone regeneration for all purposes except weight bearing. A walking caliper, without hinge, was applied and was used up to one and one-half years after operation. We would not have removed it at that time, on account of insufficient bone regeneration, but the child returned from the country, where she had been allowed to run about for several weeks without it, so we did not replace it. We intended to give postoperative deep roentgenotherapy, but most of her first year and one-half was spent in the country and she never received but two treatments. At present, she is being followed at six-month intervals with roentgenograms being taken annually. When last seen, October 4, 1939, there was one inch shortening of the left femur, for which she was wearing a half-inch lift. Function is complete. The angle of the neck is more horizontal than on the right side, and there is outward bowing and thickening of the upper third of the left femur. Bone regeneration has been slow and is far from complete. The extent of the defect has seemed to correspond to growth of bone rather than to an extension of the process, although this is open to argument. All three epiphyses at the upper end of the femur seem to have fused (Fig. 5). The patient has no complaints and is in good health. Follow-up must be continued indefinitely.

FIG. 1.—Roentgenogram showing the central chondroma of upper femur.

The case was submitted to the Registry of Bone Sarcoma of the American College of Surgeons (B.S.R. No. 1644). It is classified as osteogenic sarcoma, chondrosarcoma type, with good prognosis. Among six examiners, two classified it as benign, one diagnosed central chondroma without expression as to prognosis, and three as potentially malignant.

SUMMARY AND CONCLUSION

A case of central chondroma of the femur, nearly six years after operation, is presented. Although the microscopic appearance does not show char-

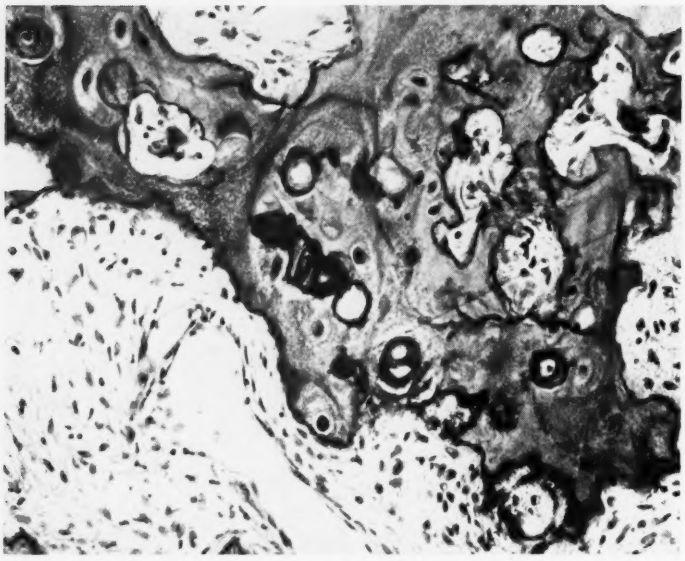

FIG. 2.—S. C. Path. No. 18990: Photomicrograph of islands of cartilage showing calcification and bone formation, also fibrous intervening stroma. (×375)

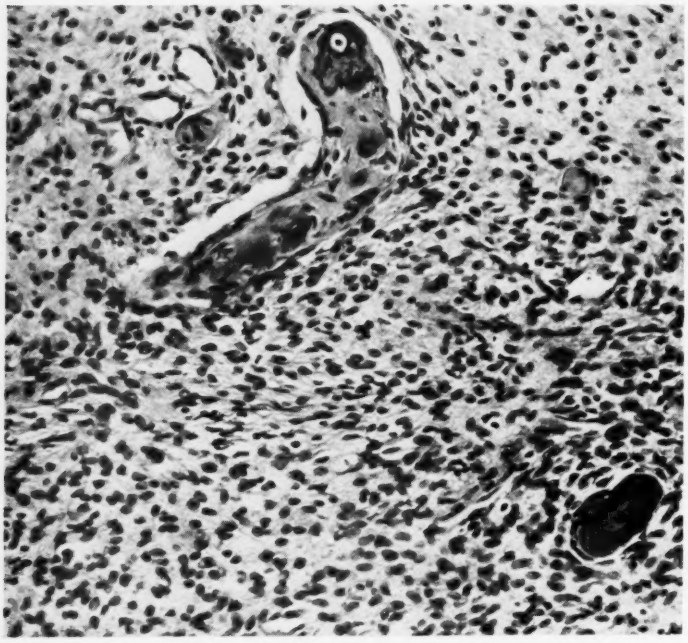

FIG. 3.—S. C. Path. No. 18990: Photomicrograph of an area showing a very cellular stroma but without mitoses. Islands of osteoid tissue. (×375)

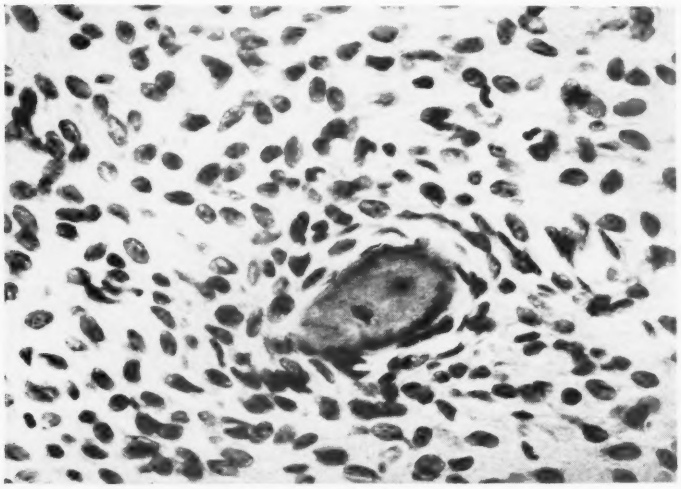

FIG. 4.—S. C. Path. No. 18990: Photomicrograph of a fibrous portion of the tumor showing island of necrotic bone. (×875)

FIG. 5.—Roentgenogram showing the result five years after operation.

acteristics of malignancy, experience teaches that these cases must be considered potentially malignant and should be followed clinically and by roentgenologic examination indefinitely.

NOTE.—Roentgenologic examination on July 8, 1941, seems to show no increased extension of the process. The patient is in excellent health at this date.

REFERENCE

[1] Geschickter, C. F., and Copeland, M. M.: Tumors of Bone. Amer. Jour. Cancer, 70–92, 1931.

DISCUSSION.—DR. PHILIP D. WILSON (New York) said that Doctor Kennedy's case was particularly interesting because it represented a diagnostic problem, both from the clinical and pathologic standpoint, and also because it represented an astonishingly good result from treatment of an osteogenic sarcoma by local curettement. Doctor Wilson said that, personally, he thought it wrong to use the term osteogenic sarcoma in a case like this, and that chondrosarcoma should be differentiated from osteogenic sarcoma. In retrospect, some points about the roentgenographic appearance of the tumor seem to be suggestive of chondrosarcoma. It was not characteristic of bone cyst or of giant cell tumor, and the appearance

of striae with bits of irregular calcification giving a kind of lobulated, trebeculated picture were typical of chrondrosarcoma.

With regard to the pathologic diagnosis, no one bone tumor is more difficult to distinguish with regard to benign and malignant characteristics than a chondroma. Doctor Wilson recalled a case that was diagnosed as a central chondroma of the humerus; yet there were three different recurrences after local operation and finally a local excision was performed followed by the insertion of a bone graft. That patient has now been well for about two years. In this case the diagnosis was a chondroma, whereas in Doctor Kennedy's case the diagnosis was chondrosarcoma and the patient has had no recurrence after local curettement—a type of treatment usually unsatisfactory with a malignant tumor. There is bound to be a good deal of disagreement as to diagnosis in a case like this. Whether the tumor is called a chondroma or a chondrosarcoma, the difference is very slight, at least from the pathologic standpoint, but in view of the subsequent course of Doctor Kennedy's case the tumor seems to have been a chondroma.

NOTICE

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The annual stipends are determined by individual circumstances and by cost of living in the location of study. The usual amount is from $1,600 to $2,400 per annum. The fellowships are granted for one year, but they may be renewed. Fellows are chosen at annual meetings of the Medical Fellowship Board in February, and applications to receive consideration at these meetings must be filed on or before January 1. Appointments may begin on any date determined by the Board.

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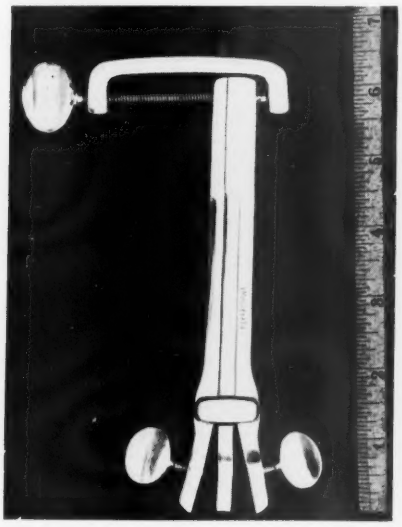
RANKIN-MIKULICZ OPERATION CLAMP

CARL R. STEINKE, M.D.

AKRON, OHIO

THE RANKIN MODIFICATION of the Mikulicz-type of colon resection employs a double crushing clamp with considerable power of compression. Doctor Fred Rankin devised such an instrument but the blades do not open sufficiently wide to allow easy entrance of a heavy colon with a thick fat mesentery. Also, it has rather long handles which are sometimes inconvenient to leave on the abdomen.



FIGS. 1 and 2.—Photographs of clamp devised for use in the Rankin modification of the Mikulicz colon resection.

The herein described and illustrated instrument made by V. Mueller and Company, of Chicago, Illinois, overcomes these disadvantages. It is simple of design and not too expensive. The clamp is six inches in length, with a crushing blade four and one-half inches long and one-quarter-inch thick. For the thick-walled bowel, with a heavy or fat mesentery, a screw-clamp applied to the distal end of the blades gives strong compression power and secures the blades when this is necessary.

This instrument may also be used as a spur-clamp in the second stage of the double-barrel procedure, similar to the clamp previously reported,[1] by opening up one blade and inserting one side of the clamp into each loop of the intestine. It has a blade one inch longer than the spur-clamp formerly devised, which is a great advantage in patients with a thick abdominal wall or long bowel loop.

REFERENCE

[1] Steinke, C. R.: Mikulicz Operation Clamp. ANNALS OF SURGERY, 93, 1117, May, 1931.

ACUTE PERFORATION OF LYMPHOSARCOMATOUS ULCER OF THE STOMACH*

REPORT OF A CASE

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INCREASINGLY frequent reports of lymphosarcoma of the stomach and the consequent gain in clarity of the clinical entity, should facilitate more successful diagnosis in the future. In spite of the rarity of the perforative lesions, three groups of these cases can be recognized in the published reports: (1) Lymphosarcomatous ulcer, perforating with the clinical picture of an ordinary perforated peptic ulcer, with a suppurative peritonitis. (2) Perforated lymphosarcomatous ulcer, with the clinical picture of a sealed, or *formes frustes* ulcer, with a transient acute peritonitis. (3) Perforation of the tumor into the surrounding structures, with or without a sarcomatous peritonitis, but without the opening of the gastric lumen into the peritoneal cavity, to produce a suppurative peritonitis.

To be sure, the literature does not always recognize the above differentiation and, as a result, the clinical concept has been somewhat confusing. Our case belongs to Group I. We have been able to find only two other such cases in the literature. The first of these was reported by Davis,[1] whose case at autopsy showed a perforation of a lymphosarcomatous ulcer on the posterior wall of the stomach, and the perforation of a similar lesion in the ileum, near Meckel's diverticulum. The second was Case 5 of Taylor's[2] series. This patient had two perforations within 13 months. At the time of the first perforation, a biopsy was taken from a regional lymph node as well as from the stomach wall. Both of these showed a typical lymphosarcoma of the reticulum cell type. After the repair of the second perforation the patient was given 1500 r. units of roentgenotherapy, and then refused further treatment. He was apparently alive and well six years later.

We have been able to find only two cases in the literature which appear to be of the second group or *formes frustes* type of perforation. One was reported by Keys and Walters,[3] in which the perforation was sealed off by the liver, and the other was reported as Cabot[4] (Case History No. 19401), in which the patient had a transient acute abdominal episode which was believed to be due to a lead colic. At a later date, an operation disclosed a lymphoblastoma of the stomach, which had apparently perforated and had become sealed off.

Of the third group there are many examples. They give rise to the statements of Eusterman and Balfour[5] that a large number of the gastric lymphosarcoma patients, who give histories of gastro-intestinal hemorrhage

Read before the Chicago Surgical Society, April 5, 1940.

have had "ulceration or perforation." Similar statements have been made by Balfour and McCann,[6] Haggard,[7] Cheever,[8] and Drane.[9]

Balfour, in a personal communication, emphasizes that the acute perforations would be observed with greater frequency in general hospitals than in clinics where most of the patients are seen only after reference. McNealy and

FIG. 1.—Roentgenogram made after recovery from the suture of the perforation, but before the gastric resection. Note the crater and filling defect on the greater curvature.

Hedin[10] have demonstrated the frequency with which carcinoma of the stomach perforates, and have suggested the biopsy of all perforated gastric lesions. It is possible that if this were carried out, more of the acute perforations of gastric lymphosarcomatous ulcers might be found.

Case Report.—Hosp. No. 24219:39: B. M., white, male, age 14, was admitted to the Cook County Hospital April 30, 1939. He stated that on the previous evening he had a sudden, sharp, steady pain just to the right of the umbilicus. One hour later he took an enema with fair results. Three hours later the pain had moved to a point in the lower right quadrant. His father gave him small amounts of whisky which aggravated the pain. He did not sleep during the night. The next morning he drank some orange

juice which he immediately vomited. At noon there was a sudden relief of pain for about ten minutes, after which it returned with increased severity all over the abdomen.

The past history was entirely negative, except that in the preceding week he had had two mild attacks of heart burn, which were relieved by soda. The family history was negative for any kind of tumor.

Physical Examination.—The patient was a well-developed, well-nourished boy who was acutely ill. Temperature 101.6° F., pulse 88. Examination was negative except for

FIG. 2.

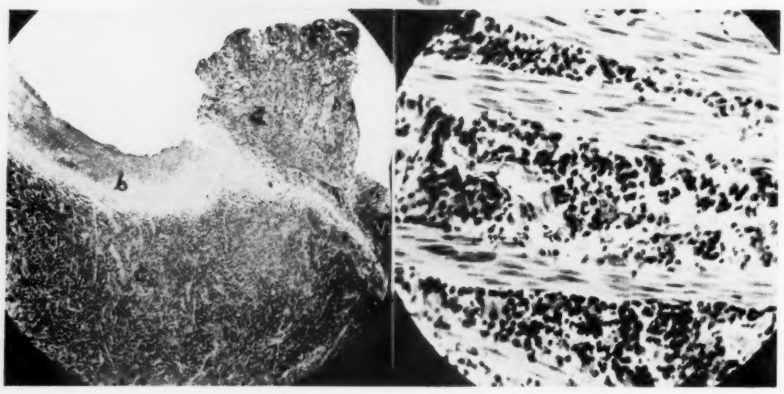

FIG. 3. FIG. 4.

FIG. 2.—Photograph of stomach removed. Note the ulcerated tumor mass along the greater curvature of the stomach.

FIG. 3.—Photomicrograph of a section of the ulcerated tumor of the stomach showing the edge of the ulcer (a) composed of gastric mucosa infiltrated with lymphocytes; also the necrotic base (b) of the mass under which are found numerous infiltrating tumor cells (c). (×36)

FIG. 4.—Photomicrograph of a section of the tumor mass involving the muscularis propria. Note the side-separation of muscle bundles by the tumor cells. (×360)

the abdomen. The abdomen was flat, diffusely rigid, and tender, but this was most marked in both lower quadrants. Rebound tenderness was diffuse. Liver dulness was normal, and the abdomen was silent during a five-minute auscultation. White blood count 25,000, of which 90 per cent were polymorphonuclear cells. The urine was normal and stool negative for blood. Because of the rapidity of the onset of the diffuse peritonitis, a tentative diagnosis of rupture of a Meckel's diverticulum was made, although a perforation at the base of an acute appendix was thought to be more likely, because of the relative frequency of the lesion.

Operation.—Under ether anesthesia, a McBurney incision was made. The peritoneum was acutely inflamed. The coils of intestine were markedly injected, and there was

a large amount of turbid fluid containing fibrin and mucus. The appendix was full of fecaliths and the serosa markedly inflamed. It was removed, and examination disclosed that the inflammation was serosal only, and secondary to the acute peritonitis. The terminal ileum was explored, but no Meckel's diverticulum found. The wound was, therefore, closed and a right rectus incision made. A perforated ulcer of the anterior wall of the stomach was found. The crater of the ulcer was about 1.5 cm. in diameter and the perforation about 5 mm. in size. Tissue was removed from the ulcer for biopsy, and the perforation closed. Biopsy was done, both because of the location of the ulcer and the age of the patient. The liver was normal and there were no enlarged lymph nodes palpable. The convalescence was uneventful.

Pathologic Examination.—Microscopic: Dr. A. Ragins. "There are small bundles of muscle tissue separated widely by large hyperchromatic cells with deeply staining round to oval nuclei. The cytoplasm of these cells is very small in amount and the cell membranes are only fairly distinct. In addition to these cells, which are in the majority, one can see eosinophils, polymorphonuclear leukocytes, which are undergoing degeneration, and a few lymphocytes. *Pathologic Diagnosis:* Infiltrating lymphosarcoma of the stomach."

Two weeks following the operation a gastro-intestinal roentgenologic study was carried out. This revealed a rather large filling defect on the greater curvature of the stomach (Fig. 1). Roentgenograms of the spine, skull and long bones did not reveal any metastases. On the 14th postoperative day, the blood count revealed a hemoglobin of 92 per cent, 4,950,000 erythrocytes, 23,200 leukocytes, of which 74 per cent were neutrophils, 2 per cent eosinophils, 18 per cent lymphocytes, and 6 per cent monocytes. Daily stools were negative for blood. The blood cevitamic acid was 0.5 mg. per cent.

Second Operation.—On the twenty-fourth day after the first operation a transfusion was administered and he was reoperated upon. At this time, the omentum was found to be adherent to the lesion. This appeared as an ulcer in the antral part of the stomach. No abnormal lymph nodes were palpable. A wide resection of the stomach was carried out, and a posterior gastro-enterostomy of the Pólya-Reichel type performed. The convalescence was uneventful, and the boy was up on the eighth postoperative day, and discharged to the ambulatory clinic on the tenth day.

Pathologic Examination.—Gross: "Specimen consists of a stomach portion measuring 13 cm. in length and 10.5 cm. in the greatest transverse diameter. On the greater curvature there is a raised, firm nodule measuring 2.5x1.5 cm., the central portion of which is ulcerated (Fig. 2). The ulcer measures 1.5 cm. by 1 cm. The base of the ulcer is light gray; the edges are firm, but are freely movable in places, and light purplish-gray in color. The folds of the stomach are distinct. The omentum is adherent to the serosal surface of the lesion. The lymph nodes are enlarged up to 20 mm. and are light yellowish-gray on section. *Microscopic:* Sections removed from different portions of the stomach were studied. Those from the serosal aspect reveal large numbers of lipoid-filled histiocytes and multinucleated giant cells in the muscularis. These cells were seen around the recent sutures. A section taken through the edge of the ulcerated tumor mass revealed a small portion of the mucous membrane infiltrated by round cells. The base of the ulcer was covered by a necrotic membrane containing cells with a distinct eosinophilic cytoplasm. Beneath the necrotic membrane are numerous lymphoid-like tumor cells which infiltrate the entire thickness of the wall of the stomach (Fig. 3). In the muscularis propria the muscle bundles are widely separated by infiltration with the tumor cells (Fig. 4).

"The perigastric lymph nodes show a marked hyperplasia with small, distinctly secondary lymph nodes. In places, however, the tissue is composed almost wholly of lymphoid cells. *Pathologic Diagnosis:* Infiltrating lymphosarcoma of the stomach."

Subsequent Course.—Since discharge from the hospital the boy has been reporting weekly for roentgenotherapy, and has been receiving 180–240 r. units through four portals. By October 25, 1939, he had received 7,200 r. units. The factors were 200 K.V., with 0.5 mm. of copper and 1 mm. of aluminum filtration. More could not be administered

because of the patient's susceptibility to roentgen sickness. At this time, he is going to school, participating in athletics, and has no complaints. He has gained 15 pounds since the operation. Repeated gastro-intestinal studies have, thus far, not revealed any recurrence.

COMMENT.—This patient represents an acute perforation of a lymphosarcomatous ulcer of the stomach, with a diffuse purulent peritonitis. It is noteworthy that the duration of the symptoms before the acute perforation was only one week. These consisted only of a mild heart burn. When the symptoms of the acute perforation occurred they were similar to those of the perforation of a simple peptic ulcer. This diagnosis was overlooked preoperatively because of the age of the patient, and because the onset, though sudden, did not appear as severe as with the usual case of gastric perforative peritonitis.

SUMMARY

(1) The term perforation is used somewhat indiscriminately in the literature of lymphosarcoma of the stomach. It would be wise to differentiate between the chronic, *formes frustes,* and acute perforations.

(2) A review of the literature has disclosed but two acute perforations, and two *formes frustes* perforations. This is in contrast to the often repeated statement that perforation is a common complication of lymphosarcoma of the stomach.

(3) Biopsy of gastric perforations may lead to the more frequent recognition of neoplastic processes as the underlying cause.

(4) A case of an acute perforation of a gastric lymphosarcoma is presented where the diagnosis was made from a biopsy at the time of operation. Successful resection was subsequently carried out.

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[5] Eusterman, G., and Balfour, D. C.: The Stomach and Duodenum. Philadelphia, W. B. Saunders Co., 1935.

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[8] Cheever, D.: Clinical Aspects and Treatment of Primary Lymphosarcoma of the Stomach and Intestines. ANNALS OF SURGERY, **96**, 911, 1932.

[9] Drane, R.: Report of a Case of Lymphosarcoma of the Stomach. Am. Jour. Roentgenol., **34**, 6, 1935.

[10] McNealy, R. W., and Hedin, R. F.: Perforation of Gastric Carcinoma. Surg., Gynec., and Obstet., **67**, 818, 1938.

FORUM

(Articles published in the ANNALS OF SURGERY *do not necessarily represent the opinions of the editors, even though they are selected and published with editorial approval. Likewise, the editors may not necessarily be in agreement with correspondents whose communications are important if only because they present stimulating opposition. Since this impartial point of view is vital to progress in science, the* ANNALS OF SURGERY *offers this forum for pertinent discussions of reasonable length.*—ED.)

Re: Abdominal Neoplasms of Neurogenic Origin:—by Henry K. Ransom, M.D., and Earle B. Kay, M.D.

AND

Diagnosis and Surgical Management of Leiomyomata and Leiomyosarcomata of the Stomach:—by Frank H. Lahey, M.D., and Bentley P. Colcock, M.D. (Annals of Surgery, 112, 700–746 and 671–686, respectively, October, 1940)

ARTHUR PURDY STOUT, M.D., NEW YORK, N. Y.:

"In the October issue of the ANNALS OF SURGERY there appear two articles on tumors of the gastro-intestinal tract, to wit: 'Diagnosis and Surgical Management of Leiomyomata and Leiomyosarcomata of the Stomach,' by Frank H. Lahey and Bentley P. Colcock, and 'Abdominal Neoplasms of Neurogenic Origin,' by Henry K. Ransom and Earle B. Kay. This latter paper discusses tumors of reputed neurogenic origin in the mesenteric and retroperitoneal regions as well as in the gastro-intestinal tract, but it is to the gastric growths especially that I should like to call attention. If one compares the illustrations in the two papers, one cannot fail to be impressed by the close resemblance between the gross appearance of the stomach neoplasms in the two groups, namely, Cases 1 (Fig. 2), 3 (Fig. 9), 4 (Fig. 12), and 5 (Fig. 15) in Lahey and Colcock's group, and Cases 1 (Fig. 9 A), 2 (Fig. 10 A), and 3 (Fig. 11 A) in Ransom's and Kay's group. Moreover, clinically, both groups show a marked tendency to ulcerate and give rise to severe hemorrhages. This similarity was remarked upon by Dr. Frederick A. Coller when discussing the two papers at the meeting of the American Surgical Association, at St. Louis, May 2, 1940.

"In my opinion, these are probably not two different tumors but are all neoplasms derived from smooth muscle, *i.e.*, leiomyomas. In order to support this contention, it will be necessary to acknowledge an erroneous opinion published by me five years ago in a paper entitled The Peripheral Manifestations of the Specific Nerve Sheath Tumor (Neurilemma), Amer. Jour. Cancer, 24, 751, 1935. When studying the occurrence of this tumor in the gastro-intestinal tract, I encountered an article by Gosset, A., Bertrand, I., and Lowy, G.: Tumeurs pédiculées de l'éstomac dites sarcomes, Jour. de chir., 23:577, 1924. This pointed out that such tumors were made up of spindle-shaped cells with a marked tendency to palisading of nuclei and they insisted that such tumors were derived from nerve sheaths. This paper influenced a number of French and some German authors and it also influenced me; so that I included three gastric neoplasms among a group of 50 neurilemmas. Since that time, I have studied a great many more neurogenic tumors from different regions, and also smooth muscle tumors of the gastro-intestinal tract, and I am convinced that the vast majority of such growths come from smooth muscle and not the tissues of the nerve sheath. Briefly, the reasons are these: Neurilemmas are encapsulated—these tumors are not. Nuclear palisading occurs just as frequently in smooth muscle tumors as it does in nerve sheath tumors, therefore, in itself, it is not diagnostic of either tumor. These gastro-intestinal tumors show no true division into solid Antoni type-A tissue and type-B tissue with its microcystic degeneration. Edema and necrosis occur in smooth muscle tumors but they do not produce the microcystic effect. Most important of all, if the tissue is properly fixed and stained, myofibrils can sometimes be demonstrated. There are other reasons, but it would unduly prolong this communication to discuss them in detail.

"These remarks apply only to gastric cases Nos. 1, 2 and 3 in Ransom's and Kay's paper. The descriptions given are perfectly compatible with smooth muscle tumors but, in my opinion, cannot be interpreted as neurilemmas. I believe that they have been misled by these tumors in much the same fashion as I was misled five years ago. Since I am confessing an error of my own, which five years of study and investigation have taught me to correct, it seemed important to me to offer this critical suggestion so that the same error will not be repeated."

SHIELDS WARREN, M.D., BOSTON, MASS.:

"We are much interested in the similarity of the illustrations in the papers, 'Diagnosis and Surgical Management of Leiomyomata and Leiomyosarcomata of the Stomach,' by Frank H. Lahey and Bentley P. Colcock, and 'Abdominal Neoplasms of Neurogenic Origin,' by Henry K. Ransom and Earle B. Kay, which appear in the October issue of the ANNALS OF SURGERY.

"We have read Doctor Stout's letter with much interest and gratification. It is important that palisading of the nuclei, frequently a property of neurogenic tumors, is not, of necessity, restricted to them. The frequency with which the nuclei of the normal smooth muscle of the stomach palisade to a striking degree is familiar to all those doing surgical pathology. Consequently, it is not surprising that palisading is also present in the tumors derived from those same smooth muscle cells. As Doctor Stout points out, the division into Antoni type-A and Antoni type-B tissue is not clearly brought out. In none of the illustrations is a Verocay body clearly demonstrated.

"While we do not deny that neurogenic tumors of the stomach may occur, we feel that at least the first three cases of Ransom and Kay are probably better classified as in the smooth muscle tumor group."

Rebuttal to the Objections of Doctor Stout

HENRY K. RANSOM, M.D. AND EARLE B. KAY, M.D., ANN ARBOR, MICH.

We are pleased to have our attention called to Doctor Stout's communication, which concerns the differential diagnosis of neurilemmas and leiomyomas of the stomach, and which presents his most

recent views on this subject. In view of Doctor Stout's painstaking studies, extending over a period of many years, his opinions should be particularly significant.

The gastric neoplasms described by us in case reports Nos. 1, 2, and 3, and to which reference is made, were classified as schwannomas or neurilemmas (Cases 1 and 2) and neurogenic fibrosarcoma (Case 3) on the basis of the following microscopic findings:

(1) The presence of palisading of a characteristic type. This has been described in great detail by Masson (Masson, P.: Experimental and Spontaneous Schwannomas—Peripheral Gliomas. Amer. Jour. Path., **8**, 367, July, 1932) and, presumably, results from the longitudinal division of the Schwann cell nuclei.

The nuclear palisades are ensheathed within anastomotic collagenous prolongations which form a syncytium which can be demonstrated by Masson's trichrome stain. Silver stains show that this syncytium is argyrophilic.

While it is admitted that nerve sheath tumors are not the only neoplasms exhibiting palisades, Masson and others contend that in those of neurogenic origin the elements of the palisade may be shown to possess the specific structure of the schwannian elements, whereas in others this cannot be demonstrated.

(2) Whorling and interlacing bands or cords of cells, the appearance of which depends upon the plane of the section through the nuclear bundles.

(3) A reticular type of architecture, found in parts of the neoplasm and which results from microcystic degeneration and edema.

When sarcomatous proliferation of these tumors occurs, the original architecture may become largely destroyed and in such cases, histologic differentiation becomes increasingly difficult. The diagnosis then often depends upon the preservation in portions of the tumor of the original architecture.

While a perusal of the literature will show that the histogenesis of the nerve sheath tumors has remained a controversial matter, the detailed descriptions given in the papers of Verocay, Masson and others, and the evidence presented by them, have seemed sufficiently convincing to warrant the acceptance of their views.

FINNEY-HOWELL RESEARCH FOUNDATION, INC.

Announcement has been made by the Finney-Howell Research Foundation, Inc., that all applications for fellowships for next year must be filed in the office of the Foundation, 1211 Cathedral Street, Baltimore, Maryland, by January 1, 1942. Applications received after that date cannot be considered for 1942 awards, which will be made the first of March, 1942.

This Foundation was provided for in the will of the late Dr. George Walker of Baltimore for the support of "research work into the cause or causes and the treatment of cancer." The will directed that the surplus income from the assets of the Foundation together with the principal sum should be expended within a period of ten years to support a number of fellowships in cancer research, each with an annual stipend of two thousand dollars, "in such universities, laboratories and other institutions, wherever situated, as may be approved by the Board of Directors."

Fellowships carrying an annual stipend of $2000 are awarded for the period of one year, with the possibility of renewal up to three years; when deemed wise by the Board of Directors, special grants of limited sums may be made to support the work carried on under a fellowship.

Applications must be made on the blank form which will be furnished by the Secretary or any member of the Board of Directors.

October 16, 1941.

BOOK REVIEWS

FELDCHIRURGIE: LEITFADEN FÜR DEN SANITÄTSOFFIZIER DER WEHRMACHT. Edited by H. Käfer, M.D., Second Edition. Dresden: Theodor Steinkopff, 1940. Price 9 Reich marks.

THE TITLE OF THIS BOOK IS "Field Surgery: A Guide for Medical Officers of the Military Forces." The book is just that! It is a pocket manual of 372 + xi pages; 5½ × 7 in. in size, written for front-line surgeons. It discusses matters of organization, transportation and general and special surgery, of interest to medical officers in the combat zone; it stops at an echelon corresponding to our Evacuation Hospital. The edition is dated September, 1940, and includes some material gathered from the rapid advance of the German armies through Poland. The announcement truly states that it is not a textbook, but a short handy guide, to enable medical officers of the line and officers surgically active in advanced units to form a rapid, reliable and comprehensive judgement of the varied and sudden measures they may be called upon to undertake. The editor and his staff of ten collaborating military surgeons have, on the whole, fulfilled their purpose admirably; some chapters are outstanding, and few are less so.

The general part contains chapters on military matters—organization, tactics, weapons and their effects, transportation—and on general field surgery (general technic in the field, first aid, infection, collapse and shock, anesthesia and hemorrhage). The second part is a concise regional field surgery, treating of wounds of the cranium, the face and eyes, ears, mouth, jaws, the neck, the chest, *etc.*

The book is so concise, meaty and full of interest, especially to those with military experience, that it is not possible to comment *seriatim*, on all its contents. Some details, however, are especially striking to the American reader.

It is noteworthy that the German Army seems still to maintain the rather divided medical echelons that it had prior to the First World War, whereas other armies have tended to omit units, or to condense them whenever possible. However, the chapter on organization does mention the need of flexibility in the establishment of various dressing stations and hospital units, and stresses the need of placing field hospitals further to the rear, which all observers in rapidly moving warfare are aware of. The statement that field hospitals are scarcely useful unless they can maintain their position for at least a week, would indicate that the author was fortunate enough to have acted mainly with advancing rather than retreating troops. The same is true of the statement that only 10 per cent of men operated upon can be evacuated on the first postoperative day, and a further 20 per cent on each of the succeeding days. It seemed to the reviewer, during his experience in the Spanish Revolution, that many wounded were more fit for evacuation immediately after operation than they were during the next two or three days succeeding.

Fölsch's chapter on general surgical technic is outstandingly good, and is evidently the product of great practical experience and adaptability. It is strange to find that he omits chloride of lime from his list of antiseptics, and that neither he, nor other collaborators, mention the Orr technic which other armies have found so useful.

The German mobile surgical team consists of eight men: 5 sterile—1 surgeon, 2 assistants, 1 instrument helper, 1 dressing helper; 3 unsterile—1 anesthetist, 1 roustabout, 1 sterilizer. Few armies will be able to afford such abundance of trained personnel!

Active immunizations against tetanus and treatment of gas and anaerobic infection are not mentioned. No mention is made of plasma transfusion; there is a short paragraph on the transfusion of preserved blood, but there seems to be no provision for blood-banks serving the front. However, a note in the section on the choice of donors would indicate

that each German soldier has his blood group determined and entered in the booklet he constantly carries on his person.

There is no space for comment on the section on Regional Surgery; it may, however, be noted that Gohrbandt's excellent chapter on abdominal injuries, although they make up less than 5 per cent of the wounds treated, is 55 pages long, while the chapter on extremity injuries, which make over 80 per cent, consists of only 26 pages. This chapter is distinctly disappointing. It is vague and lacks concrete and specific directions; it describes methods we are inclined to mistrust, or consider as antiquated; it fails to mention others (Willems' treatment of joint injuries, Orr treatment of compound fractures, etc.), which we prize highly.

On the whole the book is an epitome of those qualities that have made the German military machine so successful—direct, short, explicit, complete. One can but hope that a similar book may appear in English. This little volume, supplemented by Franz's classical small text, gives a doctor, called upon to perform military surgery in almost any position, nearly everything he need know. Weightier volumes and small systems of surgery may interest students in military schools and leisurely officers at base hospitals—but Franz and Käfer are of real use where help is scarce and urgently needed, *viz.*, at the front.

LEO ELOESSER, M.D.

SULFANILAMIDE AND RELATED COMPOUNDS IN GENERAL PRACTICE. By WESLEY W. SPINK, M. D. Chicago: Year Book Publishers, Inc., 1941.

This manual of somewhat over 200 pages contains a discussion of the sulfonamides designed primarily for the general practitioner. It fulfills its purpose admirably. It deals clearly and briefly with such fundamental problems as chemical structure in relation to anti-bacterial activity, mode of action, and pharmacologic behavior.

The main purpose, however, has been to answer the problems of choice of preparation, diseases best treated, doses and toxic effects which arise daily in practice. The local use of the sulfonamides in surgery, dermatology and dentistry is discussed. Prophylactic use in a variety of diseases is considered.

The book is written by an obviously careful, conservative and judicial author with personal experience in this field. The fact that it is concerned primarily with sulfanilamide, sulfapyridine and sulfathiazole, and has little to say of sulfadiazine or sulfalylguanidine is not a criticism but merely a limitation inherent in any book dealing with this rapidly changing subject.

KENDALL A. ELSOM, M.D.

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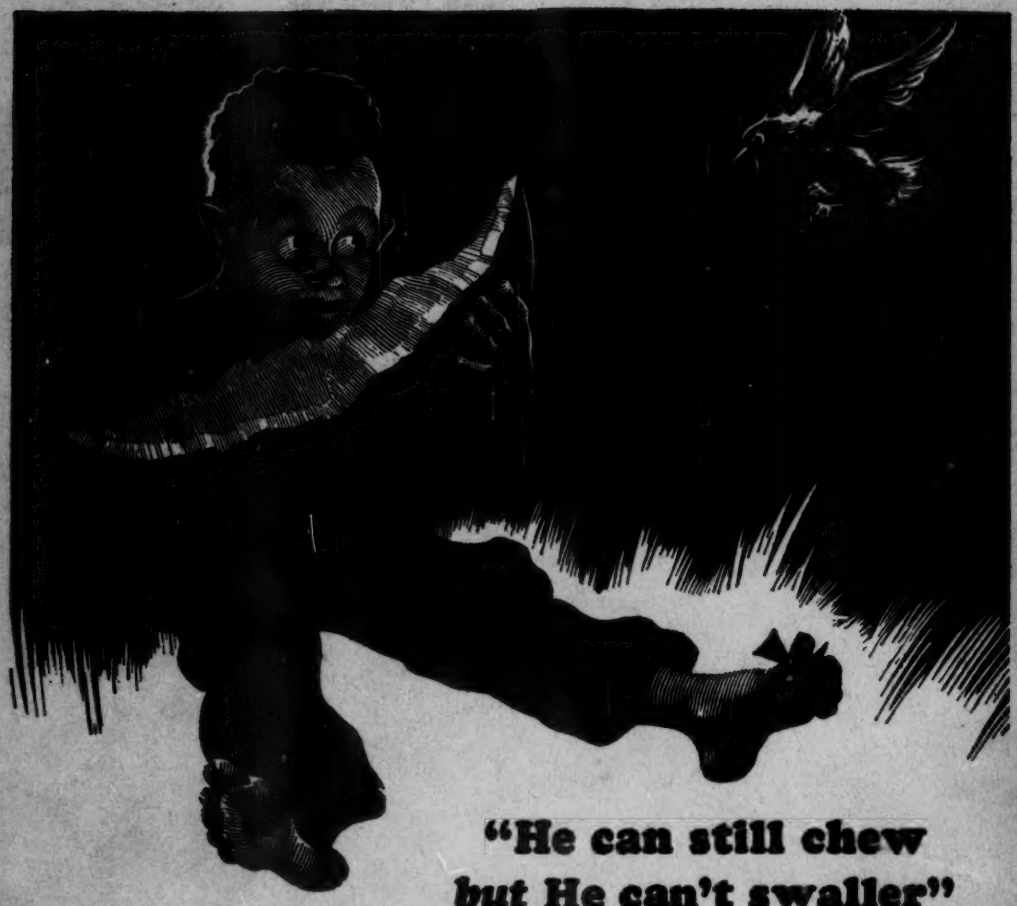

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